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FIFRA SCIENTIFIC ADVISORY PANEL (SAP)

OPEN MEETING

REEVALUATION OF THE HUMAN HEALTH EFFECTS

OF ATRAZINE:

REVIEW OF NON-CANCER EFFECTS AND

DRINKING WATER MONITORING FREQUENCY

DOCKET NUMBER: EPA-HQ-OPP-2010-0481

UNITED STATES ENVIRONMENTAL

PROTECTION AGENCY

CONFERENCE CENTER LOBBY LEVEL

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ARLINGTON, VIRGINIA 22202

SEPTEMBER 14, 2010

8:40 A.M.

FIFRA SCIENTIFIC ADVISORY PANEL

MEETING

SEPTEMBER 14, 2010

DR. JOSEPH BAILEY: We'll get started here in just a few minutes as soon as everyone gets settled.

Okay, good morning, everyone. I'm Joe Bailey, and I want to welcome everyone to this FIFRA Scientific Advisory Panel meeting. This is our third meeting this year on atrazine, and the topic for this particular meeting is the Review of Non-Cancer Effects and Drinking Water Monitoring Frequency.

I particularly want to welcome the Panel and thank them for agreeing to participate in this meeting. And I just have a word, a few quick routine administrative remarks to make. I am serving as the DFO for the meeting, and I will be serving as liaison between EPA and the Panel.

And this is a Federal Advisory Committee within the Federal Advisory Committee Act, which means that the recommendations and advice that the Panel provides to EPA is purely recommendations and advice on science issues, and all regulatory matters are strictly the Agency decisions, of course, taking into account the recommendations and advice that the Panel gives.



1 As far as the ethics regulations go, we
2 kind of review the contradict disclosure information
3 that the Panel members have provided to ensure that all
4 of our ethics regulations are complied with.

5 There is tomorrow on the Agenda,
6 beginning I believe about mid-morning, an opportunity
7 for public comment. That's one of the requirements for
8 FACA held meetings is to provide an opportunity for
9 public comment.

10 We do have a number of commenters who
11 have requested time on the Agenda to hear their
12 remarks. If there is anyone else who wishes to give
13 remarks during the public-comment opportunity tomorrow,
14 please let me know or one of the other people here from
15 the SAP office. If you have not made arrangements
16 prior to the meeting for public comments, we will ask
17 that you limit your comments to five minutes on the
18 Agenda.

19 As usual, we have a Public Docket
20 created for this meeting, and the number should be at
21 the top of everyone's Agenda. All of the background
22 documents that have been provided to the Panel so far
23 are in that document.

24 Some of them are sensitive materials
25 that you must contact the docket and sign an



1 affirmation of nondisclosure as to those; but
2 everything else should be available in the docket, and
3 that will include all of the slide presentations that
4 are made by EPA or public commenters. They are
5 enclosed in the docket very shortly after that
6 presentation, so they will be available as well.

7 And I think that covers everything I
8 wanted to bring up. Again, thank you all for coming
9 this morning, and I will now turn the mic to Chair of
10 this meeting, Dr. Steve Heeringa. Thank you.

11 **DR. STEVEN HEERINGA:** Thank you very
12 much, Joe, and welcome everyone to this 4-day meeting
13 of the FIFRA Science Advisory Panel on the topic of Re-
14 Evaluation of the Human Health Effects of Atrazine:
15 Review of Non-Cancer Effects and Drinking Water
16 Monitoring Frequency.

17 As so indicated, I am Steve Heeringa of
18 the University of Michigan. I am currently in for a
19 short period as the chair of the FIFRA Scientific
20 Advisory Panel.

21 I will be serving as Chair of these
22 proceedings with no specific substantive expertise to
23 contribute; but we have a very highly qualified Panel
24 of experts, and so we look forward to this meeting and
25 I thank them in advance and probably throughout this



1 meeting for their contributions.

2 But at this point, let's meet the Panel,
3 beginning here on my left with Ken Portier.

4 **DR. KENNETH PORTIER:** Good morning, I'm
5 Ken Portier, Director of Statistics at the American
6 Cancer Society National Office in Atlanta. I am a
7 biostatistician and member of the current Panel.

8 **DR. JANICE CHAMBERS:** I'm Jan Chambers;
9 I'm a Professor in the College of Veterinary Medicine
10 in Mississippi State University on pesticide
11 toxicology, neurotoxicology and metabolism expertise,
12 and I'm a member of the current Panel.

13 **DR. CAREY POPE:** I'm Carey Pope; I'm a
14 Professor of Toxicology at Oklahoma State University;
15 I'm a neurotoxicologist, and I'm a member of the
16 permanent Panel.

17 **DR. JOHN BUCHER:** I'm John Bucher. I'm
18 the Associate Director of the National Toxicology
19 Program at NIEHS. I'm a member of the current Panel.

20 **DR. DANIEL SCHLENK:** Good morning, my
21 name is Dan Schlenk; I'm a Professor of Environmental
22 Toxicology at the Department of Environmental Sciences,
23 University of California Riverside. My expertise is in
24 fate and effects of pesticides on aquatic organisms,
25 and I'm a member of the current Panel.



1 **DR. RICHARD GREENWOOD:** I'm Richard
2 Greenwood, a current Professor of Environmental Science
3 at the University of Portsmouth in the UK. My
4 expertise is in the area of pharmacokinetics and
5 toxicology.

6 **DR. KANNAN KRISHNAN:** My name is Kannan
7 Krishnan; I'm Professor of Occupational and
8 Environmental Health from the University of Montreal in
9 Canada. My expertise is in pharmacokinetics and
10 cytotoxicology.

11 **DR. MOIZ MUMTAZ:** Hi, I'm Moiz Mumtaz,
12 ATSDR, CDC. I'm interested in chemical mixtures.

13 **DR. NELSON HORSEMAN:** Nelson Horseman
14 from the University of Cincinnati. I'm a physiologist
15 and endocrinologist, specific expertise in mammary
16 gland biology.

17 **DR. JAMES McMANAMAN:** I'm Jim McManaman,
18 I'm from the University of Colorado; I'm Professor of
19 Obstetrics and Gynecology, and I'm an expert in mammary
20 gland biology.

21 **DR. KATHERINE ROBY:** I'm Kathy Roby from
22 the University of Kansas Medical Center in the
23 Department of Anatomy and Cell Biology, and my area of
24 expertise is female reproduction.

25 **DR. BARRY DELCLOS:** Barry Delclos from



1 the FDA National Center for Toxicological Research and
2 work in the Department of Toxicology there.

3 **DR. SANDRA LEGAN:** Good morning. I'm
4 Sandy Legan from University of Kentucky; I'm a
5 Professor of Physiology, and my expertise is female
6 reproduction and control of the LH surge.

7 **DR. WESLEY STONE:** I'm Wes Stone with
8 United States Geological Survey; I'm a hydrologist,
9 work with chemical transport.

10 **DR. RICHARD COUPE:** Richard Coupe, also
11 with U.S. Geological Survey from Mississippi.

12 **DR. HERBERT LEE:** Herbert Lee,
13 Department of Applied Mathematics and Statistics and
14 Associate Dean for Graduate Studies in Research in
15 Baskin School of Engineering. I'm at the University of
16 California Santa Cruz; I'm a statistician.

17 **DR. BETTE MEEK:** And I'm Bette Meek. I'm
18 at the University of Ottawa interchange from Health
19 Canada. I have a background in toxicology, but I've
20 worked in regulatory risk assessment in Health Canada
21 for a rather long time.

22 **DR. SUSAN AKANA:** Susan Akana from the
23 University of California San Francisco; I'm a research
24 physiologist. I specialize in hypothalamic-pituitary-
25 adrenal axis and its interaction with energy balance.



1 **DR. PENELOPE FENNER-CRISP:** Penny
2 Fenner-Crisp; I'm a private consultant, and I live in
3 Charlottesville, Virginia. My area of expertise is
4 toxicology and regulatory risk assessment like this
5 over here in the U.S.

6 **DR. ELLEN GOLD:** I'm Ellen Gold, I'm a
7 Professor of Epidemiology and Chair of the Department
8 of Public Health Sciences at the University of
9 California at Davis, and I have an interest in women's
10 reproductive health, endocrinology.

11 **DR. SHELLEY HARRIS:** Good morning, I'm
12 Shelley Harris; I'm a scientist at Cancer Care Ontario
13 and Associate Professor at the University of Toronto,
14 and I'm an epidemiologist with expertise in pesticide-
15 exposure substances.

16 **DR. JOHN BAILAR:** I'm John Bailar,
17 retired from the University of Chicago. I am a
18 physician, a Ph.D. statistician, mostly an
19 epidemiologist, and I'm currently a Scholar in
20 Residence at the National Academies here in Washington.

21 **DR. GERALD LEBLANC:** Good morning, I'm
22 Gerry LeBlanc, and I'm a Professor and Head of the
23 Department of Environmental and Molecular Toxicology at
24 North Carolina State University, and my area of
25 expertise is endocrine toxicology and I'm a member of



1 the permanent Panel.

2 **DR. STEVEN HEERINGA:** Again, thank you,
3 everyone on the Panel, obviously a very diverse and
4 deep set of scientific expertise that the Staff of
5 FIFRA SAP has again assembled for us. I acknowledge
6 their role in this, as well.

7 At this point, I'd like to open the
8 proceedings. I would like to turn to Dr. Steven
9 Bradbury, who is Acting Director of the Office of
10 Pesticide Programs at EPA.

11 **DR. STEVEN BRADBURY:** Chairman Heeringa.
12 I want to welcome the Panel members to this week's
13 meeting, as well as the public, who will be
14 participating tomorrow in our proceedings. We want to
15 thank you first for all your hard work in leading up to
16 the meeting.

17 There's a lot of information I know you
18 have been reviewing, and we appreciate the effort that
19 you've invested thus far and the investment of time and
20 your expertise during the proceedings this week and as
21 you prepare the Report in the coming months.

22 The activities of a peer-review Panel
23 such as the Panel that you're on is really critical to
24 the business of the Agency in ensuring that we got the
25 best possible scientific advice in the decision-making



1 that we have to do. It's really critical to have this
2 kind of peer-review process in place.

3 It's also important to ensure that
4 there's an opportunity for the public to provide you
5 information and insights as we proceed in evaluating
6 whatever scientific issues we have before us; it
7 supports our regulatory decision-making.

8 I just want to reaffirm the very
9 important role we play in the work of the Environmental
10 Protection Agency, in particular in the work of the
11 Pesticide Program as we not only deal with some
12 scientific issues around the pesticide atrazine but
13 more broadly around our risk-assessment approaches and
14 specific scientific challenges we take on as we go
15 forward.

16 Science is always evolving and, hence,
17 our regulatory approaches need to evolve with the
18 science. And some of the topics that we've been
19 discussing around atrazine in the past and will be
20 discussing this week and into the future tap into a
21 number of areas that are interesting from a scientific
22 perspective and also during reporting for informing
23 where we are with the science on atrazine in
24 particular.

25 Some of the discussions we've had with



1 over the last several meetings have included
2 epidemiology and how we should be trying to advance our
3 ability to use epidemiology studies in conjunction with
4 external toxicology studies and problem-formulation
5 stuff through the various stages of doing a risk
6 assessment.

7 And we'll be getting some very important
8 advice on some non-cancer issues regarding atrazine
9 during this week's meeting, which will be very helpful;
10 but it will also give us insights more broadly in terms
11 of how to use epidemiology studies as we advance our
12 risk-assessment approaches.

13 We'll also be spending some time with
14 you discussing toxicity pathways and looking at
15 different intermittent pathways and how different Modes
16 of Action can give us insights into adverse outcomes
17 and try to understand those relationships; it's very
18 important for understanding atrazine and its Mode of
19 Action and understanding adverse outcomes and how they
20 relate to different --across different levels of
21 biological immunization, very critical to ensure we
22 have the most up-to-date information around atrazine as
23 we take a look at risk assessment.

24 But those insights will be more broadly
25 applicable as we try to take advantage of the NAS



1 report on 21st Century toxicology testing and
2 integrative assessment approaches on risk assessments
3 and how it to look across different levels of
4 biological immunization and understand Mode of Action
5 that are mechanisms of action, which in turn is
6 critical for improving our ability to look at dosimetry
7 in our risk assessments and to better define what's the
8 appropriate dosimetric to use for different Modes of
9 Action at different levels of biological organization
10 and how to link this information together, both in
11 terms of the dose, delivered dose, perhaps from
12 exposure but also the duration of exposure, and our
13 understanding of Mode of Action and how that relates to
14 the timing of exposure.

15 Again, very important for understanding
16 the science around atrazine and informing our current
17 risk assessment and whether or not we need to revise
18 the current risk assessment with the insights that we
19 got from previous peer reviews and future peer reviews
20 will give us some insights more broadly as we advance
21 on risk-assessment techniques.

22 And then, of course, looking at
23 dosimetry and Mode of Action and understanding risk
24 potential from epidemiology studies or experimental
25 toxicology studies, and how do you relate that



1 information to environmental exposures.

2 In this case with atrazine, how to take
3 a look at drinking-water concentrations and
4 understanding how different changes in space and time
5 of atrazine concentration in the drinking-water sources
6 relate to that understanding we have about dosimetry
7 and temporal exposure with those and Mode of Action and
8 adverse outcomes, and how do you bring that all
9 together so that we can take a look at what's going on
10 out in the world and be confident that the current use
11 of atrazine or any pesticide down the road is safe in
12 the context of our risk assessment, what we understand
13 about dosimetry, and how that relates to temporal and
14 spatial exposure on the pesticide question, in this
15 case atrazine.

16 So a number of really important issues
17 that are very central to understanding the science on
18 atrazine, but also very informative more broadly if we
19 take a look at our risk-assessment tools in general.

20 The peer reviews that we've had thus far
21 and the ones that we'll have, the peer review we've
22 having this week and the peer review that we'll have in
23 2011 are very important in taking a look at our
24 regulatory position with atrazine and ensuring that the
25 current state of the science is still reflective of



1 what we knew about atrazine back in 2003.

2 It has been about seven years' time
3 since we did the re-registration decision for atrazine,
4 and there has been a lot of epidemiology studies that
5 have come over that time frame along with a number of
6 experimental toxicology studies done over that time
7 frame. And those studies are very important as we take
8 a look at now about five, six, seven years of intensive
9 drinking-water monitoring data that's been accumulated
10 as a condition of re-registration of atrazine.

11 And so in 2010, looking back at 2003 and
12 many years of monitoring now, the Agency felt it was
13 time to sit back, take a look at the state of the
14 science both in terms of experimental toxicology,
15 epidemiology, dosimetry in the context of sampling
16 designs for drinking water which are including making
17 sure we've got the most current science and that's
18 where we stand. I want to thank you very much at this
19 time for the group that met here in February.

20 What I would like to do now is turn over
21 the mic to Dr. Tina Levine, who is the Division
22 Director for our Health Effects Division to introduce
23 the other members of our team that have prepared for
24 the risk assessment.

25 We have had a number of folks from



1 across multiple Divisions in the Pesticide Program
2 participating in this effort, as well as colleagues
3 from our Office of Research and Development and from
4 NIEHS who have been involved in our efforts to date,
5 and I will turn it over to Dr. Levine to introduce the
6 team members and acknowledge their contributions

7 **DR. STEVEN HEERINGA:** Thank you very
8 much, Steve.

9 **DR. TINA LEVINE:** Thank you very much.
10 I'd also like to extend my welcome to the Panel and
11 echo Steve's appreciation for your time and efforts.
12 Your feedback is an important component of improving
13 the scientific foundation on regulatory decisions.

14 I would also like to thank Joe Bailey
15 and the SAP Support Team for their help in making sure
16 these meetings run smoothly and putting together these
17 wonderful Panels.

18 Let me acknowledge the OPP Team: Ms. Anna Lowit; Ms.
19 Mendez who we're very happy to see back, even though we
20 tried to keep her away; Chester Rodriguez; John
21 Liccione; Marquita King; Jessica Kidwell as well as
22 many other toxicologists in HED, along with Nelson
23 Thurman and Mary Frankenberry from the Environmental
24 Fate and Effects Division, who contributed to the
25 current Issue Paper.



1 I would also like to acknowledge the help of
2 Melanie Briscoe from PRD, who has provided a
3 significant amount of support to this effort.
4 And finally, I would like to thank the ORD Team: Ralph
5 Cooper; Susan Law, Tammy Stoker; Danielle Roddell; and
6 Jerry Goldman. Our colleagues at ORD are vital to this
7 ongoing re-evaluation, and we truly appreciate their
8 time and talents.

9 As Joe mentioned and Steve talked about, we
10 have conducted three SAP reviews this year. In
11 February we presented a Draft Framework for
12 incorporating epidemiology and human incident data into
13 our risk assessments. The February meeting included
14 two case studies involving atrazine. One of these case
15 studies looked at epidemiology studies involving
16 developmental outcomes. The same epidemiology study
17 included in the February case study will be discussed
18 today in the larger context of the total weight of
19 evidence across the non-cancer epidemiology database.

20 The second atrazine case study discussed in
21 February involved an ongoing collaborative project with
22 the principal investigators of the Ag Health Study. To
23 keep the Panel and the public up-to-date on that
24 collaborative project, we provided a short update in
25 the Appendices of the Issue Paper.



1 In preparation for April, we reviewed
2 approximately 100 experimental toxicology studies that
3 were published involving atrazine, that were published
4 since 2003, and considered a wide variety of toxic
5 effects including immunotoxicity, neurotoxicity and
6 effects on steroidogenesis.

7 At the April meeting we placed a strong
8 emphasis on Mode of Action. This involved updating and
9 reaffirming the key events related to the hypothalamic-
10 pituitary-gonadal axis, what we typically call the HPG
11 axis, which were previously supported by the SAP in
12 2000.

13 The April Issue Paper also described emerging
14 data on the effects of atrazine on the hypothalamic-
15 pituitary-adrenal axis, what we call the HPA axis. At
16 that meeting, the Panel agreed with us that the HPG
17 axis remains the major pathway for atrazine toxicity.
18 With respect to the HPA axis, we heard from you that
19 these new studies provided a biologically plausible
20 hypothesis, but that a little work needed to be done to
21 clarify existing uncertainties.

22 At the April meeting, we also presented some
23 proposed approaches for evaluating drinking-water
24 monitoring data. As you'll see from today's
25 presentation, we've taken your advice on using



1 monitoring datasets based upon more intensive sampling,
2 and we'll present a general framework for developing a
3 monitoring program tailored to the endpoints we are
4 discussing this week.

5 This week's meeting brings the topics from
6 February and April together in a single integrated
7 analysis. We'll be discussing a wide array of topics
8 such as non-cancer epidemiology, statistical approaches
9 for evaluating drinking-water monitoring and
10 pharmacokinetics. We will also hear from Dr. Sue
11 Fenton, formally of EPA and now with NIEHS, about her
12 work on atrazine and the developing mammary gland.

13 The literature review contained in the Paper
14 is current up to July 15. There have been new atrazine
15 studies published since July 15. These new papers are
16 not in the Agency's Issue Paper and will not be
17 discussed this week. We expect to hold another SAP on
18 human health effects of atrazine in 2011 to cover
19 remaining issues regarding non-cancerous risk
20 assessment and cancer epidemiology. The 2011 meeting
21 has not been scheduled. When it is scheduled, we will
22 review all studies that become available from this past
23 mid-July until approximately two months prior to the
24 meeting.

25 We look forward to your thoughtful



1 deliberations over the next few weeks, and now I'd like
2 to turn the microphone over to Dr. Anna Lowit, who will
3 begin our scientific presentations. Thank you.

4 **DR. STEVEN HEERINGA:** Thank you. Dr.
5 Levine.

6 Dr. Lowit.

7 **DR. ANNA LOWIT:** Good morning. I would
8 like to reiterate Steve and Tina's appreciation for all
9 of your time and thank you for coming. Some of you are
10 here for your third atrazine this year, and some of you
11 are on your first.

12 A couple of years ago, the NRC published
13 a couple of new reports, NAS reports. One of those
14 reports, science and physicians' reports, encourages
15 the Agency to do a couple of things and one of those in
16 particular is to make our risk assessments more useful
17 and to have more utility.

18 And the primary way to do that is
19 through problem formulation by better linking the
20 purpose and scope of the risk assessment more in line
21 with risk-management goals and needs.

22 And as you will see from the next few
23 days with atrazine, this is really an excellent case
24 study of doing that sort of thing: of focusing on
25 problem formulation across a broad spectrum of



1 scientific issues, and to think about the needs of the
2 Risk Managers as it relates to the drinking-water
3 monitoring, and to align those things in a way to
4 answer two straightforward although very complex
5 questions: do we need to do any risk assessment; and
6 to evaluate the drinking-water monitoring frequency.
7 So all those questions may be relatively
8 straightforward.

9 As you can tell from the complexity of
10 this Panel, it's a very complex set of issues.

11 You'll hear a combination. In order to
12 align the risk assessment with the risk-management
13 needs, we have a very multi-disciplinary interactive
14 team, as you will see from the presentations.

15 You will see a discussion of hazard
16 assessment around sensitive life stages, endpoints,
17 duration of exposure, but also a very detailed analysis
18 of statistics around drinking-water exposure.

19 But then at the end of the week, we'll
20 take all of those topics and will try to overlay them
21 on top of each other and think about them in an
22 integrative way of how to take durations of exposure,
23 Mode of Action, life-stage sensitivity and think about
24 drinking-water exposure and monitoring and how those
25 things come together to help think about the drinking-



1 water monitoring frequency question.

2 Prior to the 2010 review, atrazine has
3 been through the previous risk assessment has been
4 through a significant amount of peer review, starting
5 with the SAP 1988 on mammary gland tumors in rats.
6 That was followed up about 12 years later with the 2000
7 SAP which you heard Tina and Steve refer to, where the
8 key events and Mode of Action were evaluated.

9 And at that time it was really related
10 to development of the mammary gland tumor. One of the
11 outcomes of that meeting was that although those
12 mammary gland tumors in the adult rat may not be
13 relevant for human, the reproductive and developmental
14 findings from atrazine related to the Mode of Action
15 certainly are relevant for human.

16 In 2003 there was an evaluation of
17 prostate cancer epidemiology, and we anticipate in 2011
18 when we do our SAP review on cancer epidemiology that
19 we will build on that 2003 analysis.

20 You have heard quite a bit from Dr.
21 Levine. We have in this year, this is our third
22 meeting. And not to reiterate her points, but I think
23 it's worth noting that the meetings are really intended
24 to build on each other; that the February meeting was a
25 very broad meeting about framework, of how to think



1 about bringing epidemiology and experimental toxicology
2 data together into an analysis for our risk assessment
3 and to really focus on problem formulation in bringing
4 those things together.

5 We did at that time have two atrazine
6 case studies, one on developmental epidemiology
7 studies, which you will hear Dr. Christensen talk
8 about. The other one is a collaborative effort with
9 principal investigators at the Agricultural Health
10 Study. It's a project we're very excited about that's
11 moving on at a nice, steady pace that I expect you will
12 hear more about in 2011.

13 In April we focused entirely on
14 experimental toxicology data in drinking-water
15 analysis. And so today and this week, we are going to
16 bring all of it back together and talk about it in one
17 integrative week.

18 So to focus a little bit on April, just
19 to lay some of the groundwork of how we got to what's
20 in the Issue Paper and the presentations you'll hear
21 today, one of the important outcomes of the April
22 meeting was a reaffirmation of the key events related
23 to the HPG axis. Certainly we're going to I think
24 probably talk a great deal about LH, luteinizing
25 hormone, in the next few days.



1 The other important part that was
2 discussed at the April meeting was emerging data around
3 the HPA axis, and as Dr. Levine indicated, it was the
4 consensus of the Panel that although they're very
5 plausible biological hypotheses, there are still some
6 existing uncertainties in those data. And as a result,
7 the current Issue Paper in our plan right now is to
8 focus on the HPG axis as it relates to selecting
9 endpoints for risk assessment.

10 Another important point that came out of
11 the April meeting as it relates to endpoint selection
12 and thinking about durations of exposure for risk
13 assessment is that the April Panel provided the
14 conclusion that seemingly effects from corticosterone
15 and ACTH were not relevant for risk assessment.

16 And I guess the last important point
17 from April around the hazard assessment brings us to
18 the focus on LH; that at that meeting we reviewed close
19 to 100 studies on many different effects and that even
20 as of right now we're unaware of any studies around
21 immunotoxicology, neurotox, steroidogenesis or a
22 variety of other things that provide in vivo doses and
23 those relevant things eliciting attenuation of LH. And
24 that's important from a risk-assessment point of view,
25 because you want to be regulating at the most sensitive



1 level.

2 Also in April on the drinking-water
3 monitoring side, we provided a few examples of how to
4 think about evaluating data, and we proposed some
5 modeling approaches. We did hear strongly from the
6 Panel that we needed to be using datasets that had
7 higher frequency monitoring, and that has been
8 certainly you'll hear a lot about that today.

9 Okay, so how does that move us into what
10 we're going to do this week? We have reviewed a number
11 of non-cancer epidemiology studies that includes the
12 studies that were evaluated for the February meeting,
13 along with a number of other outcomes.

14 The feedback that we got from the Panel
15 in April on our reviews on how to think about those
16 studies, how to think about those studies in respect to
17 thinking of our risk assessment, was very helpful as we
18 broadened that analysis to add another influence.

19 As Dr. Levine said, Dr. Suzanne Fenton
20 will be here first thing in the morning to give her
21 presentation on her own work on the development of the
22 mammary gland. So you will not hear a presentation
23 from the Agency today on that, though she will be
24 presenting her own data.

25 There are reviews of both Dr. Fenton's



1 work and the newer study submitted by Syngenta, which
2 is one of the Coder studies, are contained in Appendix
3 A. Particularly the Rayner and the Coder studies, the
4 effects that are seen are very high doses at around 100
5 milligrams per kilogram, which is something about 50
6 times higher than the value that we have estimated for
7 our point of departure for LH.

8 The other study out of the Fenton lab is
9 a mixture study. It is what we often call the Enoch
10 study. It is unique among those mammary gland
11 development studies, in that the doses are quite low
12 and they actually include a dose lower than the LH
13 endpoint.

14 We do have some concerns about the
15 design of that study. We have concerns about how the
16 design affects the interpretation. We also have
17 concerns about how the mammary glands are evaluated and
18 how we evaluate the different dose-responses. So we
19 are really looking forward to the comments from the
20 Panel on the study design and interpretation of dose-
21 responses there.

22 Okay. So the current Issue Paper is, as
23 far as we know, and we believe this to be true, the
24 literature review is up-to-date as of July 15th. That
25 analysis, the new studies are from January 30th to July



1 15th, which is essentially our cutoff from the February
2 meeting -- excuse me, our cutoff from the April meeting
3 our cutoff from the April meeting up until the cutoff
4 for the current meeting.

5 All of those reviews are contained in
6 Appendix A, and for those of you who were here in April
7 and you looked at Appendix A and it seemed a lot of it
8 seemed the same. Well, it was actually intentional.
9 We wanted to, partly as a tool for transparency, partly
10 because we knew there would be some new members on the
11 Panel, we decided to include all of the reviews from
12 both April and the new ones in September. But
13 hopefully we had a table at the beginning, so you were
14 able to figure out what was the new part.

15 One of the really important parts of the
16 new Issue Paper is our proposals for dose-response
17 assessment. As we move out of caudal formulation into
18 a, sort of a new analysis phase, we have reviewed many,
19 many new experimental toxicology studies.

20 We've reviewed quite a few epidemiology
21 studies. And as you'll hear from Dr. Christensen, our
22 view is that those epidemiology studies, although very
23 informative for human relevance and qualitative
24 characterization, don't provide the quantitative
25 support for using in a risk assessment, so that our



1 proposal is to rely on the animal data.

2 We heard you loud and clear also in
3 April to think about doing internal dosimetry and doing
4 benchmark dose analysis, so you will certainly hear
5 about that today.

6 Another area that you'll hear from
7 Nelson Thurman and Mary Frankenberry is around the
8 drinking-water exposure analysis. That will be another
9 area where certainly the Panels from April will hear
10 that we heard your advice loud and clear and that we
11 have moved forward with that. We're proposing a
12 framework of how to think about the water monitoring.

13 Later in the afternoon we're going to
14 have two presentations on two what I like to think of
15 as integrative topics, the first one being the analysis
16 for the FQPA safety factor, and that's an integrative
17 analysis because it by statutory requirement has to
18 include both hazard and exposure together, and we'll
19 see an evaluation.

20 It is important to remember that that
21 analysis is still going on. We have not proposed an
22 update to the FQPA factor used back in 2003 in the red,
23 and we are going to wait to propose that factor until
24 there are some important toxicology studies ongoing and
25 until the drinking-water analysis is much further



1 along.

2 But we are soliciting comment from all
3 of you on the important scientific factors around
4 drinking water and hazard to think about as we move
5 forward in the coming months to complete that analysis.

6 The second multidisciplinary area, which
7 is really the crux of a lot of this, is pulling it all
8 together in one bucket, I guess, for lack of a
9 scientific word, is the implication of the toxicology
10 in the Mode of Action on the critical duration of
11 exposure.

12 And that is a very important part of
13 this whole re-evaluation, the reason being is that
14 critical duration of exposure then goes into the
15 drinking-water analysis to determine the averaging
16 time, and you'll see some from some of the
17 presentations we will rely on.

18 As we move forward in the next few
19 months and the next year, we do have some issues that
20 we will be talking with the SAP on. We will be having
21 an SAP on human health in 2011. As Dr. Levine noted,
22 it has not been scheduled yet. But at that meeting, we
23 will pick up our external toxicology literature review
24 from July 15th forward; so things that have come out in
25 the last month will be included in that 2011 review.



1 And we will follow up with proposals for
2 the duration of exposure. That's important as it
3 relates to drinking water monitoring frequency. We
4 will discuss with you our more complete analysis around
5 life-stage sensitivity as it relates to the FQPA
6 factor. And obviously, we will have a very detailed
7 analysis of drinking water at that time.

8 We'll also be talking extensively about
9 cancer, particularly epidemiology, as we await the
10 findings of a new study from the Agricultural Health
11 Study on atrazine. And at that point, we hope that
12 we'll be able to do an integrated weighted analysis
13 around cancer doing the epidemiology and the toxicology
14 more in light in the way that we've done the non-cancer
15 for this meeting.

16 So with that, this will sort of give you
17 a bird's eye view of the presentations. They are
18 largely intended to build on each other. We'll start
19 with non-cancer epidemiology, which is in my mind a
20 continuation of problem formulation. As we largely
21 focused on that in April and on experimental
22 toxicology, this is our epidemiology review in thinking
23 about how to use those data in risk assessment.

24 That presentation will be followed by
25 Dr. Chester Rodriguez, who will have a fairly lengthy



1 presentation on our proposals for dose-response
2 assessment, and many of you were here; you gave us some
3 recommendations, and we certainly took them to heart
4 and have done quite a lot of work on that.

5 After that, you will hear -- the end of
6 Dr. Rodriguez's presentation will talk about how to
7 think about the possible dosimetrics to link them to
8 drinking-water monitoring. So the natural presentation
9 after that is actually the presentation on drinking-
10 water monitoring.

11 After Nelson and Mary give their
12 presentation, I will come back and give the two
13 integrative presentations around the sensitivity, the
14 life-stage sensitivity, the FQPA factor and the
15 implications, pulling it all together to think about
16 durations of exposure.

17 And just on a personal and a
18 professional note, Dr. Elizabeth Mendez is not giving a
19 presentation today, but she has been instrumental in
20 every single one of them. And we are glad she is back,
21 even if it's just for a couple of hours.

22 **DR. STEVEN HEERINGA:** Thank you, Dr.
23 Lowit.

24 And just for the Panel and for the
25 audience, too, in terms of the proceedings today, we



1 have this set of presentations by the Scientific Staff
2 of the EPA that are scheduled for today and then
3 another tomorrow morning to start from Dr. Fenton.
4 There's plenty of time in today's schedule I believe
5 for exchange on questions and clarification.

6 It's not going to be an intense day.
7 Proceedings will become much more intense and time-
8 limited as we move into the period of public comment
9 and Charge Questions later on; it's just the way the
10 meeting is structured, and we probably can't change
11 that.

12 But at this point before we move on to
13 Dr. Christensen, are there any questions or forwarding
14 questions or clarification for Dr. Lowit based on her
15 discussion of the proceedings from February and April
16 in terms of this meeting?

17 Okay, Dr. Christensen.

18 **DR. CAROL CHRISTENSEN:** Thank you, and
19 good morning. Again, my name is Carol Christensen, I'm
20 an epidemiologist with the Health Effects Division, and
21 over the next several minutes I'll be reviewing with
22 you our evaluation of the atrazine non-cancer
23 epidemiology literature.

24 So to provide a little bit of background
25 about how we got here, previous our discussions we've



1 had with the Panel with reference to epidemiology data,
2 as well as review the purpose of our current
3 evaluation.

4 I'll touch upon in this presentation our
5 methodology or the way in which we selected these
6 studies included in our review, and I'll briefly
7 summarize those studies. Mainly we're focusing on the
8 results of those investigations and some of the major
9 strengths and limitations. Our full analysis is of
10 course presented in the written materials.

11 Looking across this database, we
12 discussed the information available to inform our, our
13 informal causal inference, including a discussion of
14 other non-causal explanations for the associations
15 observed. In synthesizing and integrating across both
16 the observational and the experimental datasets to
17 inform risk assessment, I will conclude with our
18 summary of the two, the two data streams and our
19 proposed next steps.

20 So by way of background as has been
21 mentioned, in February of this year EPA presented its
22 Framework for incorporating epidemiologic research into
23 our pesticide resistance process, and at that time we
24 articulated our attention to explicitly consider these
25 kinds of observational epidemiologic data in the public



1 formulation phase of risk assessment.

2 Very briefly, as has been mentioned and
3 just to be very clear, several studies related to both
4 fetal and perinatal outcomes were presented to the
5 Panel in February of this year and for the sake of our
6 comprehensive evaluation they are also included this
7 morning as well as the written materials.

8 And as Anna just mentioned, this review
9 reflects our assessment of the non-cancer epidemiology
10 literature as our evaluation of atrazine potential for
11 carcinogenic effects will occur in 2011.

12 So the purpose of our review again of
13 course is to identify non-cancer epidemiology studies
14 to inform risk assessment; so looking at investigations
15 of atrazine exposure in association with several
16 different health outcomes within the human population.
17 Our evaluation included assessment of the strengths and
18 limitations of each study individually.

19 This information is presented in
20 Appendix B2, as well as synthesizing and integrating it
21 across the observational epidemiology databases in
22 Section 3.0. So the results of the non-cancer epi
23 studies have been integrated with the experimental
24 database to formulate our overall conclusions and
25 proposed next steps in Section 4. Of course, these



1 will be modified by certain criteria and scientific
2 judgment as we look forward to the Panel in February of
3 this year.

4 So again back in February, the Panel
5 provided several very helpful comments to the Agency as
6 far as elements to consider for good-quality
7 epidemiology studies that are to be used to inform our
8 risk-assessment process. This wasn't by any means
9 exhaustive, but some of the key points mentioned by the
10 Panel are clearly articulating whether the study is
11 hypothesis generating or hypothesis testing in nature;
12 of course, the assessment of the validity and
13 reliability of the exposure assessment; and outcome
14 ascertainment was identified as a key factor.

15 The measurements of potentially
16 confounding variables, particularly when those
17 variables are measured in the same way between
18 comparison groups is also mentioned. And sample size
19 and statistical power, particularly the statistical
20 power to look at sub-analyses, sensitivity analyses --
21 for example, the influence of a third variable -- or
22 effect modification in the association under study was
23 also mentioned.

24 So, again, by no means exhaustive. The
25 Panel's recommendations were certainly very, very



1 helpful in the completion of our evaluation about these
2 non-cancer health effects.

3 So our literature review methodology,
4 the way in which we identified these studies, of course
5 looking for evaluations of non-cancer adverse health
6 outcomes in the open literature. We went to common
7 major/minor databases: Pubmed, Science, limited use of
8 Google Scholar.

9 We identified search criteria,
10 delineated in Appendix B1 of that material, and as well
11 as we utilized some citation mapping available through
12 Web of Science, we had hand searching of key reference
13 points and so on.

14 So we identified several hundred studies
15 initially that could potentially be included in this
16 review; however, upon review of both the title abstract
17 and the full text realized that not all of them were
18 appropriate to this question.

19 For example, some of them were really
20 exposure-only studies that did not measure association
21 with the non-cancer health outcomes, so they were
22 excluded. Several studies did not measure atrazine and
23 triazine specifically, so of course were excluded from
24 our consideration of the question today.

25 There were a handful that reflected



1 essentially case reports of acute pesticide poisoning,
2 and all very important in the literature review and one
3 instance in which the full typed document was not
4 available and several in which the studies were not in
5 fact original research but reflected editorial or human
6 opinion pieces.

7 So applying those criteria, we
8 identified 19 studies of non-cancer health effects for
9 our epidemiology literature review. So very briefly,
10 in contrast to the studies brought to the Panel's
11 attention in February of this year, the 19 studies
12 included in our lit review: several different study
13 designs, cohort case control, master case control, as
14 well as the ecologic studies presented back in
15 February.

16 In addition, it's notable that several
17 of these investigations took place within ongoing long-
18 term epidemiology studies: the Agricultural Health
19 Study; the Ontario farm family study; the Study for
20 Future Families; now they are using a vested or hybrid
21 study on childhood deficiencies and good control
22 device.

23 However, looking across the database, in
24 many instances exposures have been most limited,
25 particularly for our consideration of these in



1 quantitative risk assessments.

2 So these 19 studies can generally fall
3 into the following categories of male and female
4 reproductive health, fetal and perinatal outcomes, as
5 well as respiratory health. And the next several
6 slides kind of delineate the study results by major
7 health effects topic area.

8 So with regards to female reproductive
9 health, we identified three studies, all of which took
10 place within the Agricultural Health Study. Very, very
11 briefly, the Ag Health Study is a long-term,
12 prospective, cohort investigation of private and
13 commercial pesticide applicators in Iowa and in North
14 Carolina.

15 The study also asked spouses of licensed
16 pesticide applicators to participate in this study, and
17 in many instances the spouses are female; so that
18 comprised largely the sample population for these
19 investigations of female reproductive health hazards.

20 Some authors published an increase --
21 they observed an increased odds of long and missed
22 menstrual cycles in association with atrazine exposure
23 to atrazine or lindane users - and it should be quite
24 clear in this investigation authors were not able to
25 make an estimate of atrazine only in association with



1 menstrual-cycle characteristics; they grouped atrazine
2 or lindane users and compared that to non-users of any
3 pesticide.

4 In addition, a similar group of authors
5 a few years later published a study in which they
6 observed a delay in the timing of menopause in
7 association with ever use of atrazine over a lifetime;
8 and I should clarify that exposure was assessed by a
9 questionnaire, and the exposure metric of ever/never
10 use over a lifetime was used in these studies.

11 And excuse me, lastly, authors published
12 an elevated odds of gestational diabetes among women
13 who reported ever using atrazine over a lifetime who
14 also reported engaging in direct application of
15 pesticides during the first trimester of pregnancy. So
16 I want to be very clear that this observation was only
17 among women who reported using any pesticides during
18 the first trimester of pregnancy.

19 So looking across these three
20 investigations of female reproductive health outcomes,
21 there are several strengths as well as limitations,
22 these studies did measure atrazine exposure on an
23 individual level versus an aggregate level, all taking
24 place within the Ag Health Study, which is a large,
25 relatively highly exposed sample and is appropriate to



1 investigate this question.

2 However, as I mentioned, particularly
3 with respect to menstrual-cycle characteristics,
4 authors were not able to evaluate atrazine
5 specifically. In addition, the measurement of timing
6 of exposure is somewhat limited, again using that
7 ever/never exposure metric over the course of a
8 lifetime.

9 The frequency of assessment of menopause
10 was minimal in that investigation. Menopause is not a
11 one-time event. It occurs sometimes over several years
12 and, as the authors acknowledge, a more frequent
13 assessment of the occurrence of menopause would have
14 aided that investigation.

15 And the potential for residual
16 confounding by physical activity, both the menstrual-
17 cycle paper and the menopause paper used occupational
18 physical activity; but authors acknowledged the
19 potential for residual confounding by physical activity
20 as well.

21 So overall, these three studies we feel
22 are supportive of a hypothesis that atrazine may affect
23 the hormonal review in such a way as to possibly
24 influence reproductive health outcomes.

25 So with regard to male reproductive



1 health; we just found one study. Authors looked at
2 semen parameters in association with urinary
3 concentration of atrazine mercapturate. They never
4 calculated purely for atrazine.

5 Authors reported an eleven-fold elevated
6 odds of poor semen quality in association with atrazine
7 use, and authors defined "poor semen quality" as "sperm
8 concentration below the population median". However,
9 as you know, the observations are significantly
10 elevated but with a very large confidence interval,
11 indicating lack of precision with regard to the small
12 sample size.

13 In additional analysis within the study,
14 authors reported that individuals with more than one
15 different pesticide analyte measured in the urine were
16 more likely to have "poor semen parameters", which were
17 lack of sperm concentration, morphology and motility.

18 So in this study, the use of biomarkers
19 of both atrazine exposure and semen parameters is
20 considered a strength. The analytic techniques, both
21 the statistical and the laboratory-based techniques,
22 are sufficient to maximize the information gained from
23 this evaluation.

24 However, it does reflect a relatively
25 small sample size for some of the comparisons served,



1 and it's been noted subsequent to the publication of
2 this study that atrazine mercapturate, indeed likely
3 underestimates total atrazine exposure, researchers
4 with CDC laboratories suggest the measurement of
5 additional urinary metabolites would be fruitful for
6 future epidemiologic evaluations. And the potential
7 for confounding by other pesticides or other
8 environmental exposures is also possible.

9 So overall this one study that we
10 identified in reproductive health is suggestive of a
11 possible association; however, we need replications to
12 fully inform the nature of this association.

13 Several studies looked at fetal and
14 perinatal outcomes, two studies within the Ontario farm
15 study. The long-term investigation looked at
16 miscarriage or spontaneous abortion. Across these two
17 studies, authors recorded a 20 to 40% non-communicative
18 elevated odds of miscarriage in association with
19 herbicide and/or atrazine use.

20 These two studies, the strength of these
21 two studies include the fact that to be eligible to
22 participate in the Ontario farm family study, both male
23 and female partners in the pregnancy had to live and
24 work on the site, so it is a highly exposed population
25 to investigate this question. And as a case control



1 study, design is highly efficient and it significantly
2 reduces the possibility of recall bias.

3 However, limitation, the main limitation
4 is the essentially probabilistic nature of the exposure
5 assessment. In this evaluation, participants were
6 asked individually whether they engaged in a farm
7 activity that could have included a pesticide
8 application and separately the specific use of
9 pesticides was assessed at the farm level, not at the
10 individual level.

11 So authors assumed that those who
12 reported engaging in a pesticide activity and reported
13 use of specific pesticides were in fact the same
14 people; but it's essentially a probabilistic method of
15 exposure assessment, as acknowledged by the authors.

16 So largely because of this method of
17 exposure assessment and the fact that both the male and
18 female partners were living and working on the farm,
19 it's very difficult to isolate the influence of either
20 male or female exposures specifically in relation to
21 this fetal outcome. Also, the period of recall for
22 birth characteristics or pregnancy characteristics is
23 quite lengthy in some instances.

24 So overall, we feel these investigations
25 reflect initial evaluations of this question. Both



1 studies published over ten years ago. However, there
2 are several major limitations to consider in the
3 incorporation of these data into our assessment
4 process.

5 Similarly, we identified several
6 epidemiology investigations about birth defects in
7 association with atrazine exposure. And just to note
8 for the Panel, many of these studies or several of
9 these studies were proffered in February of this year:
10 for instance, the study by Mattix, et al., which is an
11 ecologic study we discussed back in February but very
12 briefly.

13 These authors, again using an ecologic
14 study, compared the rates of abdominal-wall defects in
15 the State of Indiana to the U.S. as a whole, reported
16 that the rates were higher in Indiana as compared to
17 the U.S. in an area of high use of atrazine.

18 Authors also reported they observed a
19 statistically significant correlation between monthly
20 concentration of atrazine in surface water and monthly
21 rates of abdominal-wall defects in the State of
22 Indiana.

23 Another study that looked at abdominal
24 wall or a type of abdominal wall defect specifically
25 was published recently in this year. In February of



1 this year Waller, et al., reported a statistically
2 significant 40% to 60% increased odds of gastroschisis.
3 Gastroschisis is one of the two major types of
4 abdominal wall defects in association with maternal
5 residence being close to an area of a high atrazine
6 USGS monitoring site. Authors define "high" as being
7 greater than the EPA limit.

8 Authors in this study also reported a
9 positive long-term exposure response relationship
10 between maternal distance from the high USGS monitoring
11 site and the gastroschisis.

12 Two other studies, also both of these
13 brought to the SAP in February of this year, looked at
14 atrazine exposure in association with several different
15 types of birth defects, so not just abdominal wall
16 defects. Winchester, et al., in 2009 reported a
17 statistically significant correlation between 11 and 22
18 different birth defects that they were able to evaluate
19 in association with the estimated time of conception
20 during the spring months versus all other seasons of
21 the year.

22 I won't recite the 11 to 22 here, but I
23 will note that the authors did not observe a
24 significant difference between the rates of
25 omphalocele, which is a second major type of abdominal



1 wall defect, in association with the estimated time of
2 conception in the spring.

3 In a second evaluation, authors reported
4 a 20% increase of lumen abnormalities among women who
5 resided closer versus further away from corn and
6 soybean fields. So atrazine exposure was estimated by
7 proximity of maternal residence to corn and soybean
8 fields in this study.

9 These authors also looked at several
10 different types of birth defects, and I will just note
11 that they observed a non-significant 50% increased odds
12 of abdominal cavity defects -- not quite the same as
13 abdominal wall defects or gastroschisis or omphalocele,
14 but I'm trying to kind of tie together across the
15 studies for you.

16 So the evaluation of these birth defect
17 investigations, several of which are hypothesis-
18 generating to suggest associations in a similar
19 direction; however, the ecologic nature of these
20 studies or these exposure surrogates which were not
21 validated are significant limitations to this dataset
22 under reporting of birth defects which we examined back
23 in February and has been given consideration in the
24 observational work on this type of outcome and
25 certainly after, after here.



1 So in conclusion, several of the
2 hypothesis-generating studies suggest that atrazine may
3 play a role in developmental outcomes; however, there
4 are several uncertainties, largely having to do with
5 the study design and the method of exposure assessment.

6 We also identified a number of
7 investigations that had adverse birth outcomes. The
8 effects were small for gestational age. Two studies
9 which looked at this question reported no association
10 when they modeled atrazine exposure over the entire
11 pregnancy period; however, when authors were able to
12 isolate atrazine exposure during specific periods of
13 the pregnancy, two investigations reported that a 20%
14 and 50% increased odds respectively if the third
15 trimester overlapped a period of high atrazine use,
16 essentially that spring/summer period in which atrazine
17 is typically used at peak levels.

18 And for the sake of completeness, I'll
19 note an ecologic study published over ten years ago
20 which reported a significant correlation between
21 residents in a county in which high atrazine levels
22 were measured on USGS sites with intrauterine growth
23 retardation.

24 Intrauterine growth retardation is
25 exactly an effect of that gene, but we suspected they



1 are probably measuring a very similar outcomes on
2 grouping them here together.

3 Some of these same authors also looked
4 at preterm-delivery and low-birth-weight adverse birth
5 outcomes in association with atrazine exposure, three
6 of which reported no significant association. One
7 study by Savitz, et al., in 1997 is within the Ontario
8 farm family study, that same study I mentioned with
9 reference to miscarriage.

10 In that same study authors reported a
11 two- to fourfold increased odds of the male partner who
12 was exposed in the preconception period. Again, this
13 is utilizing that probabilistic method of exposure of
14 living on the farm site.

15 And Villanueva also reported a 30%
16 increased odds of preterm delivery if the first
17 trimester overlaps the period by half a season,
18 essentially the spring-type period, and that was based
19 upon a sub-analysis.

20 So for low birth weight, three
21 investigations reported no association; and that same
22 Villanueva study also looked at low birth weight,
23 reported a non-significant 20% increased odds of low
24 birth weight in association with atrazine exposure.
25 And I should note both Villanueva and the Ochoa-Aku



1 study were able to measure atrazine as treated in
2 water, so getting a little bit closer to atrazine
3 exposure and water monitoring.

4 So the strength of these studies, again,
5 the two that I just mentioned, were fine measures of
6 atrazine exposure, i.e., atrazine in drinking water,
7 are somewhat consistent for the outcomes of small for
8 gestational age. Looking across these studies, both
9 the main analyses and the sub-analyses kind of give a
10 hint to critical windows of exposure. Those studies
11 are supposed to overlap at first trimester or third
12 trimester, for example.

13 However, there is still likely exposure
14 measured in air, keeping the challenges of measurement
15 exposure for this outcome, and the possibility of
16 unmeasured confounding other environmental effects that
17 can probably play a role in the association between
18 atrazine and birth outcomes.

19 So in conclusion, you can see it is just
20 a possible association with small for gestational age;
21 however, the evidence for preterm delivery and low
22 birth weight are more limited.

23 And finally, we identified one
24 investigation within the Ag Health Study. Every
25 atrazine in association with wheeze, wheeze had some



1 association associated with asthma and considered to be
2 sort of a tighter health outcome to try to measure via
3 questionnaire. Authors reported a statistically
4 significant 20% increased odds in association with ever
5 use of atrazine over a lifetime sorry, no, I'll
6 correct myself.

7 One of the strengths actually of this
8 investigation is that authors asked participants about
9 both atrazine use or all pesticide use and episodes of
10 wheeze within a similar recent time period. So this
11 comes up, these data were collected in a follow-up
12 questionnaire within the Agricultural Health Study, so
13 the questions were asked the last year or the last year
14 that you engaged in pesticide application, what
15 pesticide did you use and how many episodes of wheeze
16 did you experience. So that was a strength of the
17 study.

18 In addition, I have given you large
19 amounts of data collected in this cohort. Authors were
20 able to control for corn and grain dust and the
21 association between atrazine and these.

22 And collaborative -- that's essentially
23 a hypothesis-generating study -- atrazine was not among
24 the a priori hypotheses identified by the authors, and
25 at this time there is no biological mechanism proposed



1 to inform the nature of the observed association.

2 So this really reflects the initial
3 investigation. There are other studies and other work
4 ongoing on atrazine in specific and pesticides in
5 general within the Ag Health Study.

6 So looking across all of these data,
7 what does it say or how can it help us inform the
8 nature of the association or inform our ability to make
9 causal inference?

10 As we stated in the written materials,
11 at this time EPA cannot conclude that the associations
12 identified in the epidemiological database are indeed
13 causal in nature. The reason for this? Largely
14 because other non-causal explanations cannot be ruled
15 out or eliminated at this time.

16 As I suggested over the course of the
17 presentation, we made several biases, including the
18 possibility for exposure measurement error leading to
19 exposure. Misclassification is likely across these
20 studies; however, we feel in general the nature of this
21 misclassification would most likely be non-
22 differential.

23 With respect to the potential for
24 confounding measurement error, there are some
25 instances, particularly the measurement of physical



1 activity in the recurrent count outcomes, as well as
2 the measurement of other pesticides and other
3 environmental exposures in the analysis of these
4 particular associations that would have enhanced the
5 precision of the respective studies.

6 In addition, some of the studies, as
7 well as the sub-analyses reported within the studies
8 that are relevant to our question of use of this data
9 in atrazine risk assessment. Our sample size is
10 relatively small, relatively low; cannot rule out the
11 possibility of chance in some of our observations.

12 So synthesizing within the active
13 database of these crops to the experimental toxicology
14 database, what can we learn from this evaluation? It
15 was notable that among the comparatively stronger
16 studies within the observational epi database, there is
17 some support from the toxicology database, as we note
18 on the next slide.

19 Just within the epidemiology database,
20 investigations of female reproductive cycle
21 functioning, timing of menopause were comparatively
22 stronger studies in our opinion. Our reasons for this
23 are the authors had a priori hypotheses regarding their
24 definition of hormone-reactive pesticides, which did
25 include atrazine, so they sort of came in with prior,



1 prior knowledge or prior ideas about the nature of the
2 association.

3 The fact that in other methodological
4 work, the self-reported menstrual-cycle characteristic
5 was found to be relatively reliable, enhancing
6 measurable outcome.

7 As well within the Ag Health Study,
8 accuracy of the self-report information regarding very
9 specific chemicals have been shown to be relatively
10 higher on or at the top.

11 I'm looking at male reproductive
12 outcomes, the study by Swan, et al., in 2003. It had
13 biomarker exposure. As I mentioned, both statistical
14 and laboratory analytic methods were good.

15 And looking at adverse birth outcomes,
16 the two studies that measured atrazine exposure in
17 treated water, so closer to the actual exposure
18 profile, resulted in a relatively consistent estimate
19 for this outcome. I recall a 20% to 50% increased odds
20 in association with atrazine use if the third trimester
21 overlaps the period of higher atrazine use.

22 In addition, these studies were able to,
23 as I just mentioned, look at different periods of the
24 pregnancy, so inform a little bit better the timing of
25 the exposure, and in general the reporting of birth



1 characteristics or birth weight, the many factors that
2 go into defining this outcome have been shown to be
3 relatively reliable as well.

4 So as I mentioned, there is some
5 consistency in the experimental observations, as we've
6 heard with the female reproductive effects, male
7 reproductive effects, semen parameters and small for
8 gestational age. For example, the observation of
9 reduced pup weight in the toxicology data.

10 However, for several of the reasons that
11 I articulate here and identified throughout the
12 presentation, we feel these epidemiologic data are not
13 sufficient quality to include in our quantitative
14 assessment of atrazine. The lack of an exposure
15 response.

16 Measurement for many of these studies
17 used the ever/never use of atrazine over a lifetime or
18 atrazine concentration above or below the limit of
19 detection; plus they extended the exposure metric; lack
20 of individual-level exposure measurement in some of the
21 studies; and lack of validation for use of surrogates
22 for individual exposure is also a factor within our use
23 in quantitative risk assessment.

24 As noted, the use of the atrazine
25 mercapturate biomarker has been shown to underestimate



1 total atrazine exposure; other biomarkers are now
2 recommended for epidemiology studies. The ever/never
3 reporting of birth defects and the lack of precision in
4 most sample size were some main questions as well as
5 the sub-analyses were also important factors supporting
6 that statement.

7 So in conclusion, we feel the use of
8 these non-cancer epidemiology results will support and
9 inform our hazard characterization. As Dr. Lowit
10 mentioned, our use of these data are to be qualitative
11 and not quantitative in nature at this time.

12 These data do provide support for the
13 human relevance and the critical effects found in
14 graphs; however, on the biological plausibility, we
15 cannot link the influence of atrazine on the
16 hypothalamic-pituitary-adrenal axis specifically to the
17 recorded outcomes and the classification of the data.

18 So for these reasons and others, we will
19 continue to rely upon the external toxicology data in
20 our quantitative risk assessment.

21 So that concludes my presentation. I'll
22 be happy to take any clarifying questions. I did,
23 however, want to of course acknowledge the good work of
24 many different people on the atrazine team for the
25 review and specific integration of these data, and I



1 particularly acknowledge my colleague, Dr. Tinelle
2 Logdall, who is here with us from our Office of
3 Research and Development, who also helped respond to
4 these clarifying questions. Thank you very much.

5 **DR. STEVEN HEERINGA:** Thank you, Dr.
6 Christensen.

7 At this point, I'll put it out to the
8 Panel for questions of clarification in Dr.
9 Christensen's presentation or really the content of the
10 Issue Paper and other supporting material that we've
11 had. We got our epidemiology studies to consider. Are
12 there any questions of clarification from the Panel?

13 Dr. Bucher?

14 **DR. JOHN BUCHER:** I'm John Bucher. This
15 isn't so much clarification, but I was wondering if EPA
16 has ever attempted any kind of exposure reconstruction
17 for any of these studies.

18 **DR. CAROL CHRISTENSEN:** No. We have
19 reviewed what's available to us in the published
20 literature; we've not engaged in that kind of original
21 work ourselves at this point in time.

22 **DR. STEVEN HEERINGA:** Dr. Harris?

23 **DR. SHELLEY HARRIS:** Thanks for your
24 presentation. I just had a question on how many people
25 reviewed the individual epidemiologic studies? Was it



1 one person that reviewed all of them, or was there a
2 team?

3 **DR. CAROL CHRISTENSEN:** No, as I
4 mention in my acknowledgments, it was certainly a team
5 effort, both in the selection or the application of the
6 exposure criteria and the selection of the individual
7 studies, the 19 studies that I just went over.

8 And it was a team effort in both the
9 review of the individual studies and some of this
10 across the database and in the tox database. Typically
11 how it worked one person would sort of draft the
12 initial review, and many others would review and
13 provide comment; we had several meetings along the way.
14 So it was certainly a group effort.

15 **DR. SHELLEY HARRIS:** Was there any
16 thought given to developing some kind of scoring system
17 for those papers, the ones they reached and passed the
18 inclusion criteria?

19 **DR. CAROL CHRISTENSEN:** No, we did not
20 apply any kind of quantitative criteria for the
21 selection of these.

22 **DR. STEVEN HEERINGA:** Any other
23 questions or clarifications or exploration in regard to
24 the logic of the work that's been done?

25 Dr. Portier.



1 **DR. KENNETH PORTIER:** Dr. Bucher, this
2 is kind of an observation. As I was reading Section 3
3 in the Appendix, I kept thinking, "Well, you're telling
4 me what's really not good about these epi studies".

5 It would have been nice to see or to
6 think about what criteria would have represented a
7 really good, strong environmental epi study. I can
8 think of a lot of occupational studies where you get a
9 lot of good quantitative information that myself and a
10 number of other people at ACS, our epidemiologists have
11 this discussion all the time:

12 Well, what would make a good kind of
13 broad population study that would provide strong
14 evidence for the kind of risk assessment we're doing
15 here? And I don't get that in the report. I get a
16 feeling of what's not there, not what you would have
17 liked to have seen.

18 **DR. STEVEN HEERINGA:** Dr. Christensen, I
19 don't know if there's an answer to that. Dr. Portier
20 admitted that himself. But, feel free.

21 Any other questions or clarification
22 this morning?

23 Well, I think that again the pace today
24 will be a little more leisurely, which is good,
25 actually. It probably is a good pace, and so let's



1 take a break and at this point let's give ourselves
2 about 25 minutes, reconvene at 25 after 10:00. Thank
3 you.

4 **(WHEREUPON, a recess was taken.)**

5 **DR. STEVEN HEERINGA:** Welcome back,
6 everyone, to the second half of our first morning
7 session. To be precise, Science Advisory Panel meeting
8 on the Re-Evaluation of the Human Health Effects of
9 Atrazine: Review of the Non-Cancer Effects and
10 Drinking Water Monitoring Frequency".

11 Prior to the break we had heard from Dr.
12 Christensen in sort of an overview on the epidemiologic
13 assessment that had been done based on literature
14 review, and at this point I think we're to hear from
15 Dr. Chester Rodriguez on Proposed Updates to the Dose-
16 Response Assessment.

17 **DR. CHESTER RODRIGUEZ:** So thank you
18 very much.

19 So like he was saying, I'm going to be
20 talking about the Proposed Updates to the Dose-Response
21 Assessment for atrazine. Just to give you a little
22 background and to put in context, you know, what I'm
23 going to be talking about.

24 In the previous risk assessment to
25 support up here in the red, the approach was based on a



1 NOAEL/LOAEL. The previous study was a 6-month rat
2 laboratory study, and the key event was hormone
3 attenuation. This current re-evaluation examines new
4 science and more sophisticated approaches.

5 That includes internal dosimetry and
6 benchmark of the dose model, two of the recommendations
7 from the April 2010 report.

8 So this is what the outline looks like.
9 I'm first going to be talking about the support for
10 internal dose-response assessment. Then I'm going to
11 be moving on to the temporal aspects of plasma
12 triazines, which will then lead to a bit to a
13 comparison of LH attenuation studies of different
14 repeated dose and durations.

15 Then I'm going to move on to propose a
16 daily steady-state area under the curve as an internal
17 dosimetric. And finally, I will conclude with
18 benchmark dose modeling and some indications for water
19 monitoring.

20 So there is good reason to actually do
21 an internal dose-response assessment. In a report
22 published by the National Research Council, it was
23 cited that the dose at a target site of the internal
24 dose is the ultimate determinant of risk.

25 As we move on to apply a Mode of Action



1 approach to risk assessment, we need to be paying
2 attention to the pharmacokinetics, because that will
3 determine what internal dosimetry would that in turn
4 will lead to the Mode of Action of the key events which
5 ultimately would lead to the observed toxicity.

6 So my presentation, then, is mostly
7 concentrated on this part, the pharmacokinetics in
8 dealing with internal dosimetry. Now, talking
9 specifically about atrazine, okay, atrazine is quickly
10 and extensively metabolized as soon as it enters the
11 body through the oral route.

12 It first undergoes a first round of
13 dealkylation, mediated by the cytochrome of the P450
14 enzymes. And the result of that is the deviated two,
15 two mono-dealkylated metabolites. One is the
16 deethylatrazine, DEA; the other one is deisopropyl-
17 atrazine, DIA.

18 So the difference basically is that you
19 remove, okay, this ethyl group for this metabolite, and
20 then you remove this isopropyl group for the other
21 metabolite.

22 Another round of cytochrome P450 of
23 dealkylation then leads to the ultimate metabolite of a
24 Diaminochlorotriazine, or DACT.

25 So atrazine can also undergo a



1 glutathione conjugation by which that single chlorine
2 on the triazine ring gets substituted with a
3 glutathione residue, okay, and is conjugated, actually
4 can become part of this pathway as well.

5 So the fast metabolism of atrazine as a
6 parent chemical leads to a very short half-life in
7 vivo.

8 Now, there are no direct half-life
9 measurements for atrazine; but we can get a sense of
10 how short the half-life is from pharmacokinetic
11 metabolism studies.

12 For example, in a report by McMullin in
13 2003, it was reported that after dosing rats by oral
14 gavage with 90 mg/kg of atrazine, 30 minutes post dose
15 the parent chemical accounted for only 4% of total
16 plasma chlorotriazines, whereas that was really at more
17 than 50%.

18 Twenty-four hours post dose, the parent
19 chemical was very detectable in plasma, whereas that
20 actually was more than 98% of total chlorotriazines.
21 So these certain indications are very transient levels
22 of atrazine as a parent chemical.

23 There is another reason why there is
24 support for moving to an internal dose, dose-response
25 assessment. And that is that at least some of the



1 metabolites are also active in attenuating LH. It has
2 been demonstrated by at least two different groups that
3 that actually has intrinsic activity at intramolar
4 levels of atrazine.

5 DEA and DIA are presumed to be active at
6 the base on the intact chlorinated structure, the
7 single chlorine. Now, glutathione conjugates are
8 presumed to be inactive in this process; however, the
9 only disposition studies that we have are actually
10 based on core of the radiolabel, a radiolabel that is
11 actually from the triazine ring. Therefore,
12 glutathione conjugates need to be included in the
13 internal dosimetry.

14 So in summary, in addition to just being
15 a good thing to do to do an internal dose-response
16 assessment, we have a very short in vivo half-life for
17 the parent chemical atrazine, and the activity of the
18 chlorinated metabolites are actually good reasons to
19 use internal dosimetry in dose-response assessment.

20 So based on this, then, we're actually
21 proposing to use an internal dosimetric that is based
22 on all triazine species without having to distinguish
23 between the parent and the active metabolites. We feel
24 that this dosimetric is conservative in case none of
25 the metabolites are active. Like I said before, it's



1 actually convenient because the only pharmacokinetic
2 data that we have is actually based on this position of
3 a core of the radiolabel; that is, they don't
4 distinguish between the parent and the metabolites.

5 So now moving on, I'm going to be
6 talking then about the temporal aspects of plasma
7 triazines. For this, we paid careful attention to the
8 results of this study from the Cooper Lab, where they
9 dosed rats with a single dose of atrazine via oral
10 gavage, and the single dose was as high as 300 mg/kg.
11 And the result of the high single dose was actually
12 more this attenuation of the LH.

13 In contrast, when they tested in much
14 lower dose of 6 or lower and say 50 mg/kg/day given
15 once per day over 3 days, they almost got complete
16 attenuation with the exception of the 6-hour time
17 point. And as you can see from the results of these
18 studies, there was no NOAEL. There is no real dose-
19 response, because you get incomplete attenuation of the
20 LH response.

21 So from this study, then, we can
22 conclude that the effect is not governed by peak levels
23 -- that is Cmax -- and that it represents really a
24 repeated dosing effect.

25 So based on these two proposals that we



1 should be using total triazines for the reasons I cited
2 before and the additional observation that the
3 attenuation is not really a single dose effect, we are
4 proposing then to use as dosimetric the area under the
5 plasma concentration time curve that includes all
6 triazine species.

7 And the rationale for this is that this
8 dosimetric is really the product of concentration times
9 duration and this is a hypothetical view of a repeated
10 dosing event. So the area under this curve, then,
11 would be our proposed dosimetric.

12 So what does the plasma profile looks
13 like for triazine for repeated daily dosing? For that,
14 we turned our attention to Thede of the 1987 study that
15 was based on a C14 radiolabel of a triazine ring. And
16 as you can see, this is the triazine ring right here,
17 and all the carbons are actually carbon 14; so you have
18 the radiolabel at three different places.

19 So female rats were dosed daily for 10
20 days with a wide range of doses that included 1, 3, 7,
21 10, 50 and 100 mg/kg/day of atrazine. But actually
22 more importantly, though, plasma levels, were actually
23 monitored very frequently.

24 I think it was nearly every 24 hours.
25 And it included the elimination phase. So by far, this



1 study provides the most thorough plasma concentration
2 time profile for triazine from repeated dosing with
3 atrazine, and we just want to make that clear.

4 So now this is what the plasma profile
5 looks like. And as you can see, then, dosing started
6 time 0, and plasma levels were actually monitored
7 almost every 24 hours. So one of the things that we
8 noted right away from this profile is that the plasma
9 levels do not change much up to 96 hours; that is after
10 4 days.

11 And that is for up for the dose groups
12 1, 3, 7 and 10. For the high dose groups of 50 and
13 100, plasma levels do not change much starting at 72
14 hours; that's 3 days. And they stay pretty much
15 constant during this period of continuous daily dosing.

16 They also monitor the elimination phase
17 for each of these dose groups. This is where daily
18 dosage stopped, and these plots here represent the
19 elimination phase.

20 So I am getting more evidence of this
21 notion of pseudo-steady state, because that's really
22 what we're talking about. This quad actually looks
23 like this. When you repeat a dosing, it goes up and
24 down, up and down, and they build up until you reach
25 what we are terming pseudo-steady state.



1 So we wanted to get more evidence for
2 that. We came across this new study by Stoker, et al.,
3 where pregnant Wistar rats were dosed daily with either
4 5 or 25 mg/kg/day of atrazine either for 3 or 7 days.
5 So basically we're comparing a 3-day exposure to a 7-
6 day exposure. And plasma levels were analyzed for
7 chlorotriazines at the end of the dosing period.

8 So these are the two groups right here.
9 So for this group, then, daily dosing took place from
10 gestation day 18 through 20. For the other group,
11 daily dosing was done from gestation day 14 through 20.
12 So as you can see from the different columns, the
13 individual chlorotriazines actually vary for the two
14 exposure groups, as you can see for that for DACT, for
15 DIA and DEA. But the sum of all of these in the last
16 column, this is total chlorotriazines.

17 Now, this is the 3-day exposure group.
18 This is the 7-day exposure group. As you can see, the
19 plasma levels actually should remain the same. And if
20 you want to take into account the variability, these
21 two numbers compared to these two numbers will be the
22 same. So basically there is no difference between the
23 3-day and the 7-day exposure groups. And that is
24 consistent with this notion of pseudo-steady state of
25 the plasma levels or triazines.



1 So now I've been talking about pseudo-
2 steady state. What does it mean exactly? Well, for
3 pseudo-steady state plasma levels, plasma levels
4 actually increase upon repeated dosing until you get up
5 into a mean value, and then after that plasma levels
6 should remain pretty much the same so that they
7 oscillate around the mean value. So the magnitude of
8 this oscillations actually depends on the dose rate.

9 So the more frequent you dose, the
10 smaller the oscillation. And the oscillation will be
11 the smallest when you have an IV infusion, where this
12 would just be a line that would go like this. So as
13 you now, once you stop dosing them, you have an
14 elimination phase. But the critical aspect of pseudo-
15 steady state, at least for us, is that once you reach
16 these levels, plasma levels will remain fairly
17 constant, regardless of how long this repeated dosing
18 continues. And that is a powerful statement, at least
19 for us, because of the next slide coming up.

20 So now moving through the slide then,
21 I'm going to talk about the comparison of different
22 studies of different repeated dosing durations. So at
23 this point, then, we came up with a hypothesis. We
24 hypothesized that the level of LH attenuation will be
25 similar for studies that achieve the same level of



1 pseudo-steady state plasma levels of triazines.

2 So that's the hypothesis, and in order
3 to proceed in investigating this hypothesis, what we
4 did is we compiled all these studies where daily dosing
5 with atrazine was done for at least four days, because
6 after four days you seem to get these pseudo-steady
7 state plasma levels.

8 We expressed the attenuation effect as
9 percent control to account for the difference in rat
10 strains and inter-lab variability. We only examined
11 doses that were less or equal to 30, because after that
12 the level of the effect does not really change; you
13 seem to get a plateau after that.

14 So we concentrated on the dose range
15 after 30 mg/kg/day atrazine.

16 So these are the studies that we
17 complied. At first and foremost, we had a Cooper, et
18 al., a brand-new study, doesn't publish. It is a 4-day
19 study in duration. The mode of oral dosing was by
20 gavage, and the atrazine doses that were evaluated was
21 as follows: 1.5, 3.12, 6.25, 12.5 and 25. And the
22 NOAEL of 3.12 was established with a LOAEL of 6.25.

23 We also came across this McMullin 2004
24 study with a repeated daily dosing duration was for 5
25 days. And the doses evaluated were 0 of course, 30,



1 100 and 300. We only examined, like I mentioned
2 before, only the 30 of it, because the 100 and 300 were
3 high and they don't provide any additional information,
4 where this here is close to a plateau. There was no
5 NOAEL identified in this study.

6 We also looked at a summary of a 2001
7 study, which actually was for 1 month and covered doses
8 of 0, 2.5 and 5. We only looked at these two doses,
9 2.5 and 5, because of the same reasons that I cited
10 before. And the NOAEL for this study was actually 5.
11 Last but not lest, we looked at the critical 6-month
12 study that was used in the last risk assessment.

13 So the duration of this study is
14 actually 6 months, and the doses that were evaluated
15 were as follows: 0, 1.8, 3.65 and 29.4. The NOAEL and
16 LOAEL were 1.8 and 3.65. I just want to make a note of
17 that. because that was a critical study that was used
18 in the last risk assessment for a point of departures,
19 I think.

20 So when we plotted all these studies as
21 percent control well, actually, before getting to
22 that, let me just say a few things about the 4-day
23 study, because we're actually proposing to use it as a
24 critical study.

25 Basically, it was aimed at identifying



1 the NOAEL or LOAEL for the effect following repeated
2 daily dosing with atrazine. They used rats that were
3 regularly cycling. And the effect was evaluated over
4 the course of one full estrous cycle, which in the rat
5 is 4 consecutive days.

6 So dosing was performed via oral gavage
7 once per day beginning at 900 hours on the day of
8 vaginal estrus, and it continued on the day of diestrus
9 I and II, and it ended on the day of proestrus, at
10 which point the effect on LH was analyzed, evaluated.

11 So when we compared this 4-day study to
12 the other studies, they differed drastically.
13 Integration, this is what we saw. First of all,
14 though, this is the dose-response for the 4-day study
15 at the 1800-hour time point. That is the peak of the
16 LH surge. And like I said before, the NOAEL was set at
17 3.12 and the LOAEL 6.25 at this time point.

18 So then this is what we saw when we
19 compare the four different studies that actually differ
20 drastically, like I said before, in repeated daily
21 dosing durations. The thick line is the 4-day study,
22 and as you can see once again, you have a well-defined
23 dose-response.

24 But actually we were ecstatic when we
25 saw this, because basically you cannot differentiate



1 the NOAELs of the study. They're hard to tell, even
2 though, like I said before, they differ drastically in
3 repeated daily dosing durations.

4 And actually more importantly, I should
5 say that the single dose that we examined from the
6 McMullin 2004 5-day study was nearly on top of the 29.4
7 dose group for the 6-month study. So to me, this is
8 very remarkable that these studies are so similar.

9 So now moving on, so we covered, then,
10 the support for doing internal dose-response
11 assessment, the temporal aspects of plasma triazines,
12 and I just talked to you about comparing different
13 studies of different repeated daily dosing durations.
14 So now we're going to move on to what we're proposing
15 as an internal dosimetric. and that's a daily steady-
16 state area under the curve for total triazines.

17 So this is summary of the internal
18 dosimetric, of the internal dosimetry. I suppose that
19 it has to be based on total triazines. And the reason
20 for that is that we have a very short in vivo half-life
21 for atrazine as a parent chemical.

22 I also talked about the activity of the
23 chlorinated metabolites and the uncertainty about
24 glutathione metabolites. From this, then, we are
25 actually proposing to use the area under the plasma



1 concentration time curve as the dosimetric, based on
2 the observation that the effect is not really a single-
3 dose effect, a Cmax effect, but a repeated dosing
4 effect.

5 So the grounds, then, for selecting this
6 dosimetric is that it accounts for levels as well as
7 duration of exposure. And when you add to that the
8 steady-state condition strongly associates with the
9 effect of attenuation of the ledge.

10 And when you include, then, the
11 following repeated daily exposure, you get what we call
12 pseudo- steady state of the plasma levels of triazines
13 by the fourth day in the rat. So when you add all of
14 this up, we propose an internal dosimetric that will
15 based on the daily steady-state area under the curve.

16 So what would this dosimetric look like
17 graphically? It would actually be one of these little
18 triangles that you see in the steady-state area of the
19 plasma profile. So it will be the area under each of
20 these rectangles.

21 But this is not really rectangles. What
22 they are, I actually try this always, and that leads me
23 to the next slide. For this analysis, we used a
24 classical trapezoidal rule, okay, in a non-
25 compartmental analysis, and we also used the linear



1 elimination phase assumption.

2 So the way you do this analysis, by the
3 way, if you've never done one of these, is that you
4 estimate the area under the curve to the last time
5 point. And we have a software package that will do
6 that for us.

7 Then you take these three data points,
8 which represents the elimination phase in your product,
9 and from the slope of this line, you can estimate the
10 elimination rate constant. So then you have the area
11 to the last time point; you have an estimate of the
12 remaining area, which will be from here all the way to
13 infinity.

14 With the assumption of linear kinetics
15 then, this area for the remaining part, is actually the
16 ratio of the plasma time point here, or the elimination
17 rate constant. So basically if you want to get an
18 estimate of the area from zero all the way to infinity,
19 you basically add these two up, and that is the basis
20 of the so-called trapezoidal rule in compartmental
21 analysis.

22 So we did this for each of those groups.
23 The one that I am showing you is for the 1 mg/kg/day of
24 the dose group; but we did them all.

25 Now, when we plotted the AUC for total



1 triazines as a function of the atrazine dose -- excuse
2 me -- what we saw was a very linear relationship. I
3 mean, I could not believe that this was real data,
4 actually, after being so linear.

5 The dash line represents the 95%
6 confidence interval.

7 When we also plotted the pseudo-steady
8 state plasma levels as a function of atrazine dose, we
9 also saw a very nice linear relationship.

10 I should mention that the pseudo-steady
11 state of the daily area under the curve is just the
12 product of the steady-state serum levels times twenty-
13 four. So, these two plots are pretty much the same.
14 Except that they differ by only 24.

15 But the take-home message from this is
16 that we're seeing a linear pharmacokinetics within the
17 dose range of 1 all the way to 100. That suggests to
18 us that there are no dose-dependent changes in the
19 pharmacokinetics or total triazines that may preclude
20 the use of the daily area under the curve as internal
21 dosimetric.

22 So now, now I'm going to move on to
23 talking about benchmark dose modeling. This part of
24 the work, by the way, was done by Joanie Shione of our
25 group. And then I'm going to talk a little bit about



1 the implications on water monitoring.

2 So Joan, she did the same thing, okay,
3 that I did by compiling all the studies that could be
4 analyzed by benchmark dose model, and they started
5 studies and they came up with once again, the Cooper
6 4-day study was on top of the list on the basis that it
7 has a well-defined dose-response curve.

8 There was also a 1-month study by
9 Danelle, et al., a 1-month study by, authored by
10 Morseth, and the critical study that was used in the
11 last active risk assessment. I should, I should point
12 out that we use the Benchmark Dose Software, the latest
13 version.

14 The models that were analyzed were those
15 - okay, that are used for continuous data, like the
16 effect that we're seeing, less attenuation. These
17 other models that were evaluated -- exponential, Hill,
18 power, polynomial, linear -- the details of the
19 analysis that includes, okay, the basic criteria are
20 all in Appendix C of the Issue Paper.

21 But I'm going to talk -- but the main
22 point of this presentation, by the way, will be on the
23 Cooper of the 4-day study, since we're proposing it to
24 use it as a critical study. So like I've been
25 mentioning throughout, this study has a well-defined



1 dose-response relationship.

2 I guess you can see from the plot that I
3 showed you before, the 1800 of the time point where the
4 search of the LH actually takes place. And this study
5 also had less data variability when compared to the
6 other datasets.

7 So as for the selection of the benchmark
8 response, BMR, this is a critical issue and we'd like
9 to get input from the Panel on this. As to the BMR, it
10 is selected generally on the basis of biological and/or
11 statistical rounds.

12 I don't know what happened. Sorry, I
13 don't know what is going on there.

14 So in the absence of information
15 regarding the level of LH attenuation that could be
16 considered associated with an adverse effect, in the
17 absence of this information, then we use a BMR that's
18 based on one standard deviation from the control mean.
19 So that's a default approach in the absence of any
20 other information, and we would appreciate to get
21 feedback on that from the Panel.

22 So, BMD modeling was performed based on
23 the external dose of atrazine. The best-fit model for
24 that was exponential. The same analysis was then based
25 on steady state of the triazine levels, which you can



1 derive from the linear regression analysis that I
2 showed you before. And the best-fit model for that was
3 the Hill model. And the details of all this analysis
4 is in Appendix C of the Issue Paper.

5 So these are the results. When you do
6 the analysis based on the external dose of atrazine,
7 you come up with a BMDL of 1.96 mg/kg/day of atrazine.
8 When you do it based on steady-state levels of all
9 triazines, you come up with a BMDL of 0.65 mg/L.

10 Just keep in mind that the units of this
11 are different. And when you do the analysis based on
12 the daily steady-state area under the curve for total
13 triazine, you come up with a BMDL of 15.56 mg/L-h,
14 that's sort of the units of the area.

15 So these steady state dosimetrics, by
16 the way, can be converted back to an atrazine exposure
17 based on the linear regression analysis that I showed
18 you before. And if you do that, you come up with a
19 dose of atrazine of 1.86, and you get the same results
20 for these two because they're pretty much the same,
21 like I mentioned before; they just differ by 24. So
22 these dosimetrics, then, may be used to establish a
23 point of departure, and we'd like to get input from the
24 Panel regarding this analysis.

25 Now so as of the whole point behind this



1 work, one of the main points I'm just saying is to try
2 to refine the drinking water monitoring frequency.

3 Now, this is a hypothetical water
4 chemograph. It's not pretty-looking; I mean, it's
5 hypothetical, but this is realistic based on the shape.
6 So how will you use, then, the results of our analysis
7 to analyze something like this?

8 Well, on the next slide, we came up with
9 two approaches that you can use. First, you can use a
10 drinking water of the rolling average value for a time
11 period of concern, and that can be compared to a point
12 of departure that is based on external dose of
13 atrazine.

14 This is in line with the current
15 approach, actually, that's in place right now. It's
16 set to the time period; it's actually 90 days. So
17 you're seeing a 90-day rolling average.

18 As a second approach, though, you can
19 compare an average daily concentration of triazines to
20 steady-state levels of triazines, or you can even
21 compare the area under this water chemograph over a
22 period of concern and you can compare that to a daily
23 steady-state area under the curve.

24 So those are two possible approaches
25 that we came up with, and we'd like to get input from



1 the Panel whether that's good or bad, I guess.

2 So given the linear relationship between
3 steady-state triazine levels and external dose of
4 triazine, the potential levels of concerns can be
5 related back to an atrazine exposure. So the
6 observation that we're seeing, linear kinetics, is a
7 very good thing that will simplify the analysis.

8 So this is just a summary slide, a
9 conclusion slide, if you will. So I talked to you
10 about the basis of doing an internal dose-response
11 assessment that includes all plasma triazines, parent
12 as well as metabolites.

13 I talked about the temporal aspects of
14 plasma triazines and the effect, LH attenuation. Both
15 of these actually support the use of a daily steady-
16 state area under the curve for triazines. We use
17 benchmark dose modeling that was based on steady-state
18 dosimetrics of total triazines as well as external dose
19 of atrazine.

20 And we feel that our analysis will give
21 very valuable perspectives for refining water
22 monitoring frequency, and of course we'd like to get
23 feedback from the Panel on the impact of this analysis.

24 So with that, I will conclude my
25 presentation. Thank you.



1 **DR. STEVEN HEERINGA:** Thank you, Dr.
2 Rodriguez.

3 At this point, I'd like to open it up to
4 the members of the Panel for any questions or
5 clarification either on Dr. Rodriguez's presentation or
6 the corresponding material in the Issue Paper.

7 Dr. Bailer?

8 **DR. JOHN BAILAR:** There's a great deal
9 of information here. It's a kind of information that
10 I'm not really familiar with in a direct personal way,
11 so I may have missed something.

12 But I am very much impressed by the
13 regularity of the dose-response curve, even at the
14 lowest positive dose, which was not statistically
15 significantly different from the control.

16 This suggests to me that an approach
17 might be developed that is closely related to how we
18 deal with carcinogens, which I know a good bit more
19 about; that is, in the process of considering
20 regulation, to consider what would be an de minimis
21 risk and then proceed from that, rather than from what
22 appear to be the NOAEL and the LOAEL.

23 **DR. STEVEN HEERINGA:** Thank you, Dr.
24 Bailer.

25 Others?



1 Dr. Schlenk.

2 **DR. DANIEL SCHLENK:** Yeah, just a point
3 of clarification. Are you through this presentation
4 moving away, then, from a PBPK model? Is that kind of
5 the idea that I'm getting, because it seems that you're
6 kind of going with this AUC sort of thing, and I'm just
7 curious. Can you just fill me in a little bit more on
8 why you are deciding to go away from the PBPK?

9 **DR. CHESTER RODRIGUEZ:** Okay. So the
10 reason why we're moving away from a PBPK model is
11 because there is no reliable PBPK model. So the ideal
12 approach here would actually involve a PBPK model; but
13 that's not the only pharmacokinetic analysis that you
14 can do.

15 You can use non-compartmental analysis,
16 which is what we use, and actually derive actually very
17 useful information from that. So you don't have to
18 have a full PBPK model to actually make use of
19 pharmacokinetic information.

20 **DR. DANIEL SCHLENK:** Just to follow up;
21 so, again, will you be pursuing a PBPK model in the
22 future, or is that sort of a dead end, I guess?

23 **DR. CHESTER RODRIGUEZ:** If one becomes
24 available absolutely, because, you know, when you have
25 a PBPK model you can extrapolate across different



1 routes of exposure, across different species, high-
2 dose, low-dose, absolutely. So if one actually becomes
3 available, absolutely we'll use it.

4 **DR. STEVEN HEERINGA:** Dr. Lowit?

5 **DR. ANNA LOWIT:** Yes, just one point I
6 have on the timing issue. Dr. Rodriguez has actually
7 reviewed the PBPK models and our reviews of that are in
8 the Appendix. There's a timing issue just to keep in
9 mind. One of the things that we always like to say is
10 that because of the nature of atrazine we're always
11 cognizant of what is going on in the literature, and we
12 always keep up with the literature.

13 But there's a goal within 2011 to create
14 whether or not to make a choice around the drinking
15 water monitoring and whether we need to do any risk
16 assessment, and it appears extremely unlikely in that
17 time frame for that existing PBPK model to be upgraded,
18 and peer-reviewed for that matter, to use.

19 So the hope is to have a less
20 sophisticated but still informative approach to looking
21 at internal dosimetry.

22 **DR. STEVEN HEERINGA:** Dr. Chambers and
23 Dr. Lee.

24 **DR. JANICE CHAMBERS:** I'm kind of
25 confused about one of the things you alluded to several



1 times. You're talking about a dose-response curve on
2 the Cooper, et al., study of 2010 actually in slides 56
3 and 57

4 **DR. CHESTER RODRIGUEZ:** Yeah.

5 **DR. JANICE CHAMBERS:** and I just don't
6 see where you're saying dose-response with those
7 standard errors or standard deviations. What dose-
8 response have you.

9 **DR. CHESTER RODRIGUEZ:** What dose-
10 response?

11 **DR. JANICE CHAMBERS:** There's no-effect
12 and there's effect, and it just looks like the no-
13 effect levels are all together with the levels of
14 standard errors and the effect levels, all of it like
15 they're not different from one another. So where is
16 the dose-response curve?

17 **DR. CHESTER RODRIGUEZ:** The dose-
18 response is actually based on that 4-day study. I'm
19 sorry, I guess I'm not following your question closely.
20 Are you confused about why you compare so well to the
21 other studies?

22 **DR. JANICE CHAMBERS:** Look at graph 56
23 so I can see it.

24 **DR. CHESTER RODRIGUEZ:** Okay, give me a
25 second.



1 Okay, it's this one; 56, yeah.

2 **DR. JANICE CHAMBERS:** Oh, okay, all
3 right. I don't quite see what you're talking about is
4 the dose-response there, because the standard errors
5 suggest that there's the 3.12 and the low was all the
6 same statistically, and the 6.25 above is all the same,
7 right?

8 **DR. CHESTER RODRIGUEZ:** No, actually.
9 Based on the statistics that was done on this, the 3.12
10 excuse me, the 6.25 is actually very different from the
11 control. So that's why the NOAEL was set at 3.12 and
12 the LOAEL at 6.25. And so these statistics that was
13 done I believe was on a 0.05 confidence okay, p-value
14 if you will. But the benchmark dose modeling is based
15 on one standard deviation from the control mean.

16 Okay, does that answer your question?

17 **DR JANICE CHAMBERS:** No, not at all.
18 Let me try again.

19 **DR. ANNA LOWIT:** Dr. Chambers, let me
20 try. I think it may be helpful to look at slide 57
21 again, because that's the overlay of the four studies
22 on top of each other. I think if you look at the
23 pattern, you sort of look from the bend in Cooper data
24 around the doses around six and to the left, and then
25 six and higher.



1 I can see your point, actually; as you
2 think about below six, there across those four studies
3 there's actually across four studies it's remarkable
4 that similar dose is that low; but I think it's in the
5 nature of this kind of data that you see those kind of
6 error bars. But it is also clear from this plot that
7 the dark black line from the Cooper data has much
8 stronger dose-response characteristics than did the
9 other studies.

10 But then if you look at you start to
11 get in the medium doses because we haven't really
12 plotted the really high ones on the graph, it's six to
13 higher; you can see it, you can really begin to see a
14 plateau. And if you continue the if Dr. Rodriguez had
15 continued to plot the doses greater than 30, because
16 several of these studies have that, you would see that
17 the plateau is almost completely flat at or around the
18 25% attenuation.

19 **DR. CHESTER RODRIGUEZ:** Right. And
20 actually, one of the reasons why, I mean, I didn't
21 include the higher doses is because you will not get to
22 see them at this region in the low dose, which I think
23 is critical. When you have different studies that
24 differ up dramatically in dosing but yet the NOAELs and
25 the LOAELs are hard to distinguish, that to me is



1 remarkable and

2 **DR. STEVEN HEERINGA:** Dr. Bailar?

3 **DR. JANICE CHAMBERS:** I'm sorry.

4 Dose-response implies to me that you get
5 more response with higher doses and all, and everything
6 from 6.25 across there with those standard errors looks
7 like it's the same and the things that you're looks
8 like the dose-response curve below that, you're saying
9 is all NOAELs and therefore not an effect. So I really
10 just don't understand.

11 **DR. STEVEN HEERINGA:** Dr. Bailar and Dr.
12 Portier on this one, and then we'll switch.

13 **DR. JOHN BAILAR:** Oh. This PowerPoint
14 reinforces my concern about the use of NOAELs. There
15 are, what, six points there that are labeled NOAEL?
16 Every one of them was below control.

17 What's the probability that would occur
18 by chance alone, even though the individual points may
19 not be statistically significantly different than
20 control? I think there's, you know, a real indication
21 that there's something going on in that area that's
22 labeled NOAEL.

23 **DR. STEVEN HEERINGA:** Dr. Portier and
24 then--

25 **DR. KENNETH PORTIER:** Well, I just



1 wanted to respond to Dr. Chambers' point. I think what
2 EPA is doing here is model-fitting and then join a
3 conclusion from the model-fitting that there's a dose-
4 response pattern, and this is given in Figures 5.9 and
5 5.10 in the white paper.

6 So they're not doing pair-wise
7 comparisons, you're right. If you look at the 25 and
8 you look at the 15, they overlap and you say there's no
9 difference. But when you step back and actually fit a
10 curve to this; there is a significant fit.

11 The Hill curve fits, and the Hill curve
12 suggests that a small change in dose produces a small
13 change in response, and I think that's what they're
14 basing their risk assessment on a more model-fitting
15 exercise rather than a dose-comparing, and that's why
16 they're trying to get away from this NOAEL, you know,
17 kind of making this point, this dose is significantly
18 different from this other dose. The model says a small
19 change produces a small response, and the Hill model is
20 the one that they are basing it on.

21 **DR. CHESTER RODRIGUEZ:** Thank you.

22 **DR. STEVEN HEERINGA:** Dr. Legan.

23 **DR. SANDRA LEGAN:** Thank you, Sandra
24 Legan.

25 With regard to the comments that have



1 been made and a couple of other things that I'm aware
2 of about LH surges, I'd like to just ask a couple of
3 questions.

4 Yes, there's a large degree of
5 variability around these data points, and that is
6 probably almost certainly due to the fact that these
7 data were taken from one time point, the 1800-hour time
8 point. And that is generally over a group of animals,
9 the peak time of the LH surge under these photoperiodic
10 conditions.

11 However, it's important to remember that
12 if you look at any LH surge data in any species, the
13 peak time at the peak is very variable in terms of the
14 levels. So this is simply the nature of the data;
15 that's our problem, especially with small changes in LH
16 peaks that you're talking about in terms of their
17 attenuation at low doses of atrazine or any common
18 disruptor.

19 In having said that, though, I'm a
20 little bit concerned with the fact that you see a
21 plateau, as you've pointed out, at higher levels. And
22 no dose there, shown at least up to 30 mg/kg/day, has
23 suppressed the amplitude of the LH surge more than
24 about, what, 40%, 50%, let's say; is that right? Maybe
25 60% at most. It turns out that physiologically, well,



1 only maybe 20% of the LH-surge total amplitude is
2 required for fertility in the female rat.

3 So the LH surge is a very large release
4 of pituitary hormone that is overkill as far as the
5 fertility of the animal is concerned. So I think we
6 need to keep that in mind, because as one of the
7 previous Panel members mentioned, the Hill equation or
8 the analysis is going to talk about very small changes
9 in the amplitude of a physiologic hormonal release, and
10 these small changes in amplitude will have essentially
11 no effect on the reproductive function of the female
12 rat. Even down to 50% or 60% of the loss of this
13 released hormone, they'll still ovulate their full
14 complement of ova, and they will be fertile. So I
15 don't--

16 The other thing is that if you're
17 talking about at doses of 30 milligrams and beyond, out
18 to 100 I think was on the subsequent graphs with the
19 linear relationships for the benchmark dose analysis.

20 If there's no further suppression of the
21 LH surge -- and as Dr. Chambers pointed out so well, it
22 plateaued if they're all the same after that, that I'm
23 not sure I understand how more atrazine exposure could
24 be detrimental, even to the rat.

25 I mean, there's no dose, all the way out



1 to 100 mg/kg. Well, that I can see from attenuating
2 the LH surge, is going to affect the fertility of the
3 rat.

4 And then having said that, the last
5 comment is if you have a plateau beyond 30 mg/kg and
6 you didn't use the third--you didn't use those two
7 higher doses in the analysis, the first analysis of the
8 dose-response that we just saw slide 55 or 56; but
9 those doses are added on to the benchmark analysis.
10 And they're not part -- I don't think they're part of
11 the dose-response, what dose-response you have up to
12 30.

13 So could you address those issues a
14 little bit, especially the latter one?

15 **DR. STEVEN HEERINGA:** Dr. Cooper, I see
16 you've come to the microphone. I assume that you've
17 been singled out to address this.

18 **DR. RALPH COOPER:** As soon as the
19 questions get hard and somebody throws something at me.

20 Ralph Cooper, USEPA.

21 I think some of the points you make are
22 right spot-on; but what I think is a little confusion
23 here and Chester put this slide up, they stopped in the
24 previous slide. I don't know how you can go back to
25 the one we had where you did your analysis where you



1 stopped at 30 and you have the plateauing take place,
2 okay? Then you're focusing on, if you look at that, it
3 stopped at 30. If you look at the data that we
4 submitted right here, just stop here a moment -- you
5 see we stopped at 75.

6 What you're seeing there is I don't know
7 what the difference is between 6.25 and 25; but as you
8 increase the dose beyond 75 -- and that's what I think
9 this slide that Chester brought up with the blocks on
10 it shows that 100 dose does bring it down statistically
11 different.

12 If you compared the 100 to the 12 you
13 would see it was lower to the point where the higher
14 doses are even right at baseline to the analyst. So
15 you can get back down to baseline with the higher
16 doses.

17 In this 4-day exposure, though, that's
18 the pattern that was observed. And I guess it's mostly
19 where it was shallow dose-response that's there, it's
20 just that it was locked off in his analysis. And
21 there's been --

22 **SPEAKER:** Well, have we seen is that 75
23 through their data?

24 **DR. RALPH COOPER:** That right there is
25 the same.



1 **SPEAKER:** 25.

2 **DR. RALPH COOPER:** Oh, I'm sorry, it's
3 25. We don't have it on here now.

4 **SPEAKER:** So there wasn't any data like
5 that in the Issue Paper, either.

6 **DR. RALPH COOPER:** Yeah, 75 isn't here.
7 We eliminated it.

8 **SPEAKER:** In this one.

9 **SPEAKER:** Figure 5.9, Figure 5.9 shows
10 the 75 dosimetric.

11 **DR. CHESTER RODRIGUEZ:** Yeah. So we
12 were actually concentrating on doses that were below
13 30. And the rationale for that is that that was the
14 highest dose in the 6-month study.

15 So just to be able to compare studies,
16 then we concentrated on that, on the range. And we
17 also felt like the higher doses, I mean, the human
18 relevance actually goes down, you know, because it's
19 unlikely that a human would get exposed to 50 or 100
20 mg/kg. So I think this is more relevant in the context
21 of human health of the risk assessment.

22 **DR. STEVEN HEERINGA:** Okay. Now we go
23 to Dr.--

24 **DR. RALPH COOPER:** I didn't hear his
25 answer.



1 **DR. STEVEN HEERINGA:** Oh, sure.

2 **DR. RALPH COOPER:** The second part of
3 your question, Dr. Rodriguez. These studies were done
4 with young adult female rats that have amplitude, LH
5 surge amplitudes at, in our lab anyway, at 20, 27, 30
6 milligrams per mil, and that's somewhere probably. as
7 you mentioned, the 80% excess in the amount of LH
8 that's, quote, unquote, "needed" for ovulation. So the
9 females will in this particular instance, you wouldn't
10 anticipate there would be any disruption of ovulation.

11 We chose the 75 as our highest dose
12 based on previous work that showed that 2 weeks of
13 dosing with 75, they stopped cycling. So, again, it is
14 this cumulative effect kind of thing that we were
15 working with, that in one cycle you may not see an
16 adverse outcome but continued dosing may eventually
17 manifest itself.

18 The second thing is that this is perhaps
19 in the 2000 SAP, the concern about atrazine and LH was
20 brought up because of the extended exposure bringing
21 about premature reproductive senescence.

22 And you know in the middle-aged female
23 that amplitude of that LH peak is not at 30. It's
24 down; it could be as low as 10. So now a small
25 decrease might actually drop them below the ovulatory



1 quota. So that's what the framework that we were
2 working is in those studies.

3 So you're correct in saying that I
4 wouldn't anticipate an adverse outcome of a single-
5 cycle exposure like this. And we're looking at that,
6 because one of the things is as you raise up the dose,
7 you saw fewer animals showing the expected proestrus
8 here. So there's something going on there but we just
9 don't know what, we haven't got the values yet.

10 But these lower doses here are just, as
11 we said in my thing, predictors for changes that are
12 occurring that are, that bode some type of adverse
13 outcome if dosing was extended.

14 **DR. STEVEN HEERINGA:** Dr. Legan, follow-
15 up?

16 **DR. SANDRA LEGAN:** Thank you.

17 I agree with your comments about the
18 fact that you might not see this effect over a single
19 cycle. Have you done in regard to what you said just
20 now, have you done a comparison of when the LH surge
21 actually drops below a certain amplitude, like below
22 about an 80% suppression, and the timing of when the
23 cycles stop, because in order for the effect on the LH
24 surge to be meaningful in terms of the treatment or the
25 effect of atrazine on it, that has to coincide.



1 They can't just miss cycles when the LH
2 surge is suppressed after 75. What was it, 2 weeks at
3 75 mg/kg, I mean those things, the timing has to be
4 just right to be able to make that conclusion.

5 **DR. STEVEN HEERINGA:** Dr. Lowit.

6 **DR. ANNA LOWIT:** I think there was one
7 more piece of your question that hadn't been answered
8 yet, the part around when we did our benchmark dose
9 modeling as part of what's in Appendix C. The 75 mg/kg
10 dose was used in that analysis, so even though it's not
11 on this graph, the 75 dose was used in those
12 calculations.

13 **DR. SANDRA LEGAN:** It's on slide 62 and
14 63, 50 and 100 were used, not 75 I think; am I right?
15 And I don't know where -- that was part of the
16 question, why you're including those and where I guess
17 those doses were in the total atrazine where you
18 labeled disappearance data.

19 **DR. RALPH COOPER:** But the doses --

20 **DR. STEVEN HEERINGA:** Dr. Cooper?

21 **DR. RALPH COOPER:** The doses that were
22 submitted in that internal report that's in the Docket
23 had the 75, and it had the full day of proestrus
24 changes of the characterization of surge in all of the
25 dose groups at all the time points, and this one was



1 pulled out of that quota dataset; so I don't know.

2 **DR. ANNA LOWIT:** Dr. Legan, I think it's
3 important to keep in mind there are two sets of
4 quantitative calculations here. There is the set of
5 calculations that Dr. Rodriguez has the lead on around
6 pharmacokinetics, particularly with the Thede study,
7 looking at--what place--around slide 60 that that
8 pseudo-steady state graph.

9 Then there is a separate set of
10 calculations, primarily done by Dr. John Liccione, that
11 are contained in Appendix C that are benchmark dose
12 modeling estimate calculations, and they're important
13 distinctions, because the T-study is looking at plasma
14 concentrations over a wide range and then the benchmark
15 dose modeling is intended to derive a point of
16 departure for assessment purposes. They're certainly
17 interrelated as you think about using the internal
18 dosimetrics, but they are two separate sets of
19 calculations.

20 But in the benchmark dose modeling, the
21 75 dose was used?

22 **DR. STEVEN HEERINGA:** Figure 5.9 on the
23 Issue Paper shows that one.

24 Dr. Krishnan, and then Dr. Greenwood.

25 **DR. KANNAN KRISHNAN:** Just a couple of



1 clarifying questions, too. This relates to slide 63.

2 Can I see slide 63, please? Yeah.

3 I was looking at the model part of it. I
4 just want to make the point that zero dose doesn't
5 correspond to zero AUC here, it's like that's suggested
6 by the equation more rather than the details and
7 origin. So is it like it takes a 0.7 mg/kg or
8 something to have zero AUC, or am I misreading
9 something here?

10 **SPEAKER:** I have no idea, actually.

11 **DR. CHESTER RODRIGUEZ:** I think you're
12 right, actually. One way of actually doing this thing
13 of integration is to force it through zero. I didn't
14 do that. I just felt like, you know, we may lose some
15 information when you force it to zero, and I just
16 wanted to get a sense of what the Y intercept would be
17 without modifying the data too much by forcing it
18 through the origin.

19 **DR. KANNAN KRISHNAN:** And the second q
20 of clarification is that the total dose or the
21 equivalence that you calculated, was it always adding
22 milligrams to milligrams, or in any of the cases would
23 you do an equivalence based on millimoles? In other
24 words, if you have data on the metabolites, one would
25 do millimoles using their molecular weights, add them



1 up, and then once you have total millimole then
2 multiply it with the atrazine molecular weight to have
3 the atrazine equivalence.

4 So my question is has any attempt of
5 calculations and computation based on the molecular
6 weights of the individual metabolites and atrazine
7 done, or was it just simply adding milligrams all the
8 time straight?

9 **DR. CHESTER RODRIGUEZ:** It was simply
10 adding actually milligrams. We just felt that the
11 molecular weights, you know, are so similar, and what
12 you're really looking are actually radiolabeling
13 equivalence. So it really doesn't matter what the
14 species is as long as it has the radiolabel. So that
15 was the basis for just adding milligrams.

16 **DR. STEVEN HEERINGA:** Dr. Greenwood, do
17 you want to talk?

18 **DR. RICHARD GREENWOOD:** I may be missing
19 something here, but if you're giving the same dose for
20 4 days, given that you've got an almost perfect
21 regression line between dose and area under the curve,
22 is there really that particular area under the curve?

23 I mean, I may be missing something here;
24 but it's easier to measure the dose than the area under
25 the curve, so why would you use area under the curve?



1 I mean, you said it's more useful; but I don't see why
2 if you're going to give the same dose 4 days.

3 **DR. CHESTER RODRIGUEZ:** Right, so

4 **DR. RICHARD GREENWOOD:** Sorry.

5 **DR. CHESTER RODRIGUEZ:** No, that's okay.
6 That goes back to the figure that I showed you before,
7 what a single high dose had a very modest effect,
8 whereas a much smaller dose, but even for at least 3
9 days, had a very pronounced effect. So that actually
10 suggests to me at least that duration of exposure is
11 actually critical, okay? And on that basis, then the
12 area under the curve is justified as an internal
13 dosimetric.

14 **DR. STEVEN HEERINGA:** That would be
15 slide 46 that shows that.

16 Dr. Lowit?

17 **DR. ANNA LOWIT:** Adding to what Dr.
18 Rodriguez said, I think the observation you've made
19 about the linearity of the lines at steady state,
20 because I think what Dr. Rodriguez basically just added
21 to that was that steady state is the required event for
22 these linear lines. We've asked ourselves that
23 question, too, Dr. Greenwood, and I think there's a
24 couple of ways to think about this. It's certainly
25 something that we'd like to hear your feedback on.



1 From a simplicity standpoint, it would
2 appear from those lines that doing the sort of matching
3 of rolling-average water concentration to an
4 administered dose of atrazine is actually a pretty
5 reasonable thing to do; that's what those graphs would
6 suggest.

7 As we think about, as you hear Nelson
8 Thurman's presentation later, one of the important
9 questions that we'll be asking in the coming months is
10 the adequacy of the current monitoring data. And to
11 understand peaks that we don't have in the current
12 dataset, data peaks, we have peaks in certain datasets;
13 but had you had more monitoring, theoretically they
14 could have been higher.

15 Something that we've talked about is
16 that these area-under-the-curve metrics may help
17 provide conceptual help interpretation of some of that
18 work that Nelson will be doing in the coming months.

19 And so by using the AUC metrics in those
20 I don't know the right term, because Nelson is not
21 sitting here to tell me the right term; but as we move
22 through those statistical analyses to evaluate that,
23 the AUC metric may help us interpret missing piece in a
24 theoretical way easier than will be rolling averages
25 that can be a little bit hard to get your mind around



1 what exactly are the rolling average of a week or two
2 weeks or three months, or six months for that matter.
3 So that's something to think about.

4 **DR. STEVEN HEERINGA:** Dr. Akana.

5 **DR. SUSAN AKANA:** I'm interested in the
6 idea of the pseudo-steady state, and this is a
7 measurement of all the radiolabeled core. But is it
8 correct that there are different bio efficacies of
9 atrazine versus some of its metabolites like that?

10 **DR. CHESTER RODRIGUEZ:** To my knowledge,
11 there is no information on the relative activities of
12 the metabolites compared to the parent. So in the
13 absence of that information, I think it's justified to
14 use total plasma triazines.

15 **DR. SUSAN AKANA:** I'm not sure, but I
16 thought I recollected SAP to earlier this year that
17 that had a very different effect on the HPA axis and
18 some of the other metabolites and atrazine itself. So
19 I'm not pointing to LH. It may have some other effects
20 on other hormone systems that are not being recognized.

21 **DR. STEVEN HEERINGA:** Dr. LeBlanc.

22 **DR. GERALD LEBLANC:** Gerry LeBlanc.

23 Continuing on that line concerning
24 pseudo-steady state, based upon the information we see
25 and I think it's reasonable to assume that a pseudo-



1 steady state atrazine is not predominant triazine and
2 that among the dealkylated products, that is the
3 dominant triazine. I was wondering if you know
4 anything about GSH conjugates, whether to what
5 proportion they exist as pseudo-steady states?

6 **DR. CHESTER RODRIGUEZ:** I can say that
7 based on mass-balance pharmacokinetic studies,
8 glutathione conjugates can account up to 30% of the
9 metabolism, and of course you'd only have one, right?
10 You have at least four glutathione conjugates. They
11 are presumed to be not active because of the lack of
12 the chlorine on the triazine ring. But, actually,
13 there is no information actually to support that that
14 I've seen.

15 So by using, then, total triazines we
16 feel we are being conservative, just in case some of
17 the metabolites are active or not active. But in the
18 absence of relative activity information, I think this
19 is the best approach.

20 **DR. STEVEN HEERINGA:** Dr. Bailar.

21 **DR. JOHN BAILAR:** I'd like to hear a
22 little more about why you consider this a conservative
23 approach. I can imagine situations in which it might
24 be quite the opposite.

25 **DR. CHESTER RODRIGUEZ:** Quite the



1 opposite in what sense, I mean?

2 **DR. JOHN BAILAR:** In the sense that if
3 it's a single complement of the total that's the bad
4 actor, you could be diluting that effect by throwing in
5 all the others.

6 **DR. CHESTER RODRIGUEZ:** Right, that is a
7 possibility. But in the absence of that information, I
8 think this is the best approach. This is the current
9 state of the science.

10 **DR. JOHN BAILAR:** I think that's, you
11 know, a reasonable position, but I'd be happier if you
12 said something more about it.

13 **DR. CHESTER RODRIGUEZ:** You have a very
14 good point, thank you.

15 **DR. STEVEN HEERINGA:** Dr. Lowit.

16 **DR. ANNA LOWIT:** I think it's important
17 to keep in mind there have been a couple of comments
18 now about the metabolites that there are normal
19 metabolites, and there is very little dose-response
20 data for anything but the administered dose to
21 atrazine.

22 There's...Susan Mollis, who sits behind
23 me, has done some outcome data with some of the
24 metabolites. There is certainly some DACT data out of
25 the McMullin lab and there has been a couple of other



1 groups. But it's, it's sparse, the dose-response is
2 generally very poor. So we don't want to over-
3 interpret that data.

4 **DR. STEVEN HEERINGA:** Dr. LeBlanc?

5 **DR. GERALD LEBLANC:** I don't know if it
6 needs to be said, but just to follow up on John's
7 comment, you referred to your approach being a
8 conservative approach, and I see it as a conservative
9 approach. I mean, you're looking at total triazine
10 internal dose without any consideration of which
11 component is toxic, which component isn't toxic; so it
12 seems reasonable to me, as well.

13 **DR. STEVEN HEERINGA:** Additional
14 questions or clarification for Dr. Rodriguez's
15 presentation before we conclude?

16 I think Dr. Portier has one question.

17 **DR. KENNETH PORTIER:** Oh, I have the
18 naive question of the day. When you talk about liter
19 there, is that the liter plasma internal dose or is
20 that liter water administered dose? It's not clear in
21 the documentation and you switched back and forth in
22 the discussion, so I got lost.

23 **SPEAKER:** Right.

24 **DR. STEVEN HEERINGA:** Dr. Rodriguez.

25 **DR. CHESTER RODRIGUEZ:** Are you talking



1 about the units?

2 **DR. KENNETH PORTIER:** On the --

3 **DR. CHESTER RODRIGUEZ:** Yeah. So these
4 are liters of blood, right, so that's actually the
5 units of the area under the curve are units of
6 concentration times time, right? It's easy to account
7 levels, that's more or less duration, and that's why
8 you see that hour at the end. But, yeah, we're talking
9 about plasma levels.

10 **DR. STEVEN HEERINGA:** Dr. Lowit.

11 **DR. ANNA LOWIT:** At this point in time,
12 we have not actually taken any of the internal
13 dosimetric data and linked it to any of the water data;
14 so I'm sorry if we weren't explicit in some of those
15 metrics. We haven't actually made that connection yet.

16 **DR. STEVEN HEERINGA:** Okay. Well, it's
17 been I think a productive start, and we've got a long
18 way to go. What I'd like to do at this point unless
19 there are additional questions from Panel members for
20 Dr. Rodriguez, Dr. Lowit or Dr. Cooper, why don't we
21 take a lunch break, and we're scheduled to return here
22 at 1:15.

23 So we'll see everybody back at 1:15 for
24 two additional sessions this afternoon, and again I
25 think that the pace of these sessions will be very



1 favorable. We'll have time to ask questions and make
2 sure everybody is clear on the content and look forward
3 to the afternoon.

4 Everybody, see you at 1:15.

5 **(WHEREUPON, a luncheon recess was taken.)**

6 **DR. STEVEN HEERINGA:** Good afternoon,
7 everyone. Welcome back to the afternoon session of our
8 first day of our FIFRA Science Advisory Panel Meeting
9 on the topic of the Re-Evaluation of the Human Health
10 Effects of Atrazine: Review of Non-Cancer Effects and
11 Drinking Water Monitoring Frequency.

12 At this point we are in the process of
13 hearing the formal scientific presentations that
14 accompany the Issue Paper, and we heard this morning
15 from Dr. Christensen and Rodriguez, and I think at this
16 point we are going to be turning to the issues related
17 to the evaluation of water-sampling strategies and the
18 frequency of monitoring, and I think Nelson Thurman and
19 Mary Frankenberry.

20 **MR. NELSON THURMAN:** Okay, so we're
21 transitioning from toxicity to exposure, and the reason
22 we're focusing on the drinking water is that for
23 atrazine drinking water is the major contributor to
24 aggregate exposure of human health. So it's important
25 for us to have a reliable estimate of that drinking-



1 water exposure.

2 And while I'm the one talking here, Mary
3 Frankenberry was instrumental in helping put all the
4 report together and putting this together; so it's a
5 team effort, so it's not just the guy talking.

6 Some of the conditions of re-
7 registration for atrazine included some monitoring
8 programs. One focused on community water systems for
9 human health, and the requirement was to monitor those
10 community water systems that through quarterly Safe
11 Drinking Water Act monitoring were above a certain
12 concentration. Those are considered to be the more
13 vulnerable systems for monitoring.

14 The program was designed to provide an
15 exposure estimate for a 90-day period of concern. So
16 there was weekly monitoring during the time frame when
17 you most expect to find atrazine in the waters,
18 generally beginning sometime in April and running
19 through August more or less, depending on the time and
20 the area.

21 There was a second monitoring program
22 that's focused on ecological exposure and particularly
23 impacts of atrazine on aquatic plant communities. That
24 monitoring tend to be up toward the headwater streams.
25 You're going to hear me refer to information and



1 lessons we've learned from both of those programs.
2 We've had, this is the second SAP that has focused on
3 the human-health part of the community water-system
4 monitoring and how that relates to the human health
5 assessment. Most of this focus of that SAP and this
6 has been on the frequency of monitoring: how frequently
7 do we have to monitor to capture the exposures of
8 concern.

9 There were two other SAPs, one in
10 December of 2007 and a followup in May of 2009, that
11 looked at the ecological effects exposure. The focus
12 in that one was primarily more of a spatial rather than
13 temporal, but there was some sampling frequency
14 involved in that, but it was more or less looking at
15 what contributes to vulnerable systems.

16 And so you'll hear me refer to both, but
17 those are the SAPs that we have addressed before.

18 And so as a quick recap of some of the
19 monitoring issues that we raised at the SAP. Like I
20 mentioned, the original monitoring design looked at was
21 based on providing exposure estimates for a 90-day
22 period of concern. It looked at weekly sampling during
23 that.

24 You've heard some of the presentations,
25 and we may end up with a different duration of concern



1 as a result of our deliberations, and it leads to the
2 question: Weekly sampling was adequate for a 90-day
3 duration of concern. If we have a shorter duration,
4 how adequate is that existing monitoring? Do we need
5 more monitoring, or can we provide some type of
6 confidence bounds or possibly even a safety factor that
7 could account for the differences, based on the
8 monitoring?

9 And I will point out that these
10 questions, where we're focusing on atrazine, these
11 questions have broader implications for other
12 pesticides as well. How much can we derive from
13 existing less frequent sampling, and how frequently
14 does sampling have to be to adequately characterize the
15 various exposures?

16 The main points we heard from the
17 September SAP regarding monitoring, the biggest one
18 was, well, to design a study you really need to know
19 the duration of concern, because honestly once you know
20 that it's easy to design a study, given whatever
21 confidence bounds you need.

22 For shorter durations, the estimates of
23 the peak exposures become more critical. For longer
24 duration, obviously it's less critical. We haven't
25 determined what that duration of concern is yet, but



1 we're looking at approaches that will work fast once we
2 have that in place. And we realize that one approach
3 may work better for short duration of exposure and
4 other approaches may be adequate for longer duration,
5 so we may be looking at more than one approach,
6 depending on where we end up.

7 The SAP was concerned that some of the
8 presentations we were looking at community water
9 systems that had weekly sampling intervals, and the
10 concern was those weekly sampling intervals may be
11 missing some short-term peaks and may be excluding out
12 some of the variability and providing a biased
13 representation of the actual concentration profiles.

14 The best set of more intensively sampled
15 data, which would include either daily or near daily
16 sampling during the time when we are likely to find
17 atrazine, is actually for ambient waters not
18 necessarily associated with the source water, the
19 community water system. Some of them we are looking
20 primarily at Heidelberg College's data.

21 Some of them are on rivers and streams
22 that are large enough to support a community water
23 system, if they don't. Some of them, like some of the
24 atrazine ecological exposure, are in the headwaters and
25 generally farther upstream than most of the community



1 water systems, although there are some smaller systems
2 that are not too far off from that.

3 So we'll talk a little bit more about
4 what we're looking at in that regard and our proposal
5 for how we think we would use that. And one of the
6 other things, the SAP recommended combining a
7 regression-based model such as USGS's watershed
8 regression on pesticides with creating random function
9 models.

10 They also suggested looking at extreme
11 value theory. We've taken a closer look at some of
12 those approaches, and we're going to follow up on that.
13 We provided some information in the background paper on
14 that.

15 For today, we're going to focus on three
16 main issues that we're bringing for you related to
17 monitoring, and I want to point out that I can't count
18 that should be Questions 4.1, 4.2 and 4.3 up there.

19 So we're briefly going to touch on a
20 framework for monitoring studies based on
21 recommendations from the SAP and some of the lessons
22 we've learned.

23 We're going to talk to you a little bit
24 more about what intensively sampled datasets we think
25 we can use and how we propose looking at them, and then



1 we're going to follow up with some of the approaches
2 interpreting monitoring data based on the feedback we
3 have from the April SAP.

4 So to begin with, this is, I guess when
5 you work on it for a while and work on some of these,
6 some of this starts to seem like common sense; but it's
7 probably a pretty good idea to capture down in writing
8 so that we have a chance to take a look at it.

9 We're looking and what we provide is a
10 framework for what we would describe more as targeted
11 monitoring study. You are not likely to be able to
12 monitor everywhere a pesticide occurs. So what we want
13 is to have a monitoring study that focuses on the area
14 where the pesticide is most likely to be found.

15 Models like WARP or other spatial data
16 layers can be used to identify vulnerable sites, not
17 just in pesticide use but also folding in some of your
18 hydrologic soil, weather factors that would drive
19 exposure.

20 In the same manner you're not
21 necessarily likely to sample throughout the year, you
22 may not need to sample throughout the year; but what
23 you want to do is target your intensive sampling during
24 the period where you're mostly likely to find the
25 pesticide in water, which is going to be at or around



1 the time when it's likely to be applied and then for
2 several, depending on the mobility and the half-life of
3 the pesticide, for a period of time afterwards.

4 For something like atrazine, which is a
5 pre-emergent herbicide, it's pretty easy to define that
6 time frame. For other pesticides, it may be a little
7 more difficult; but it is a way to focus that
8 monitoring.

9 The sampling frequency needs to be based
10 on the toxicological exposure duration of concern,
11 sampling more frequently if you've got a short duration
12 and less frequently if longer duration. What you want
13 to see here is you need to balance the cost of the
14 study with the needed accuracy that you need.

15 And one of the reasons we're looking
16 closely at the intensively sampled data is we want to
17 be able to, depending on your sampling frequency, can
18 we provide some type of confidence bounds that you're
19 likely to get in a monitoring study or, alternatively,
20 can we provide some type of a safety factor that can be
21 used to address with less frequent monitoring.

22 One of the recommendations came out in
23 the last SAP was consider using auto-samplers to
24 collect the data for exposure periods of interest.
25 We're seeing more use of auto-samplers; it's still not



1 commonly used for at least the pesticide monitoring we
2 see, but we do see it being used a little bit more
3 often as the technology improves.

4 There are a couple of ways you could do
5 that. One is to use it to fill in for events in
6 between your regularly sample intervals. For instance,
7 you might have a flow triggering, so if you have a
8 runoff event that it triggers increase in flow.
9 Another way may be to use auto-samplers to collect
10 regular intervals over your time period of concern so
11 that you end up with a time-integrated average over
12 that time period. So there's a couple of ways of
13 looking at that.

14 And the idea, the concept of possibly
15 using auto-samplers to integrate over the time period
16 of concern plays into what Dr. Rodriguez was talking
17 about in terms of looking at how do we relate
18 monitoring to an area under the curve approach where we
19 may not need to capture every single peak, but what we
20 need to do is capture what that exposure is over that
21 duration of concern.

22 Now, targeted monitoring isn't new, and
23 I think what we've seen with atrazine is a pretty good
24 example both in the community water system and in the
25 ecological exposure, a pretty good example of how that



1 can be applied.

2 For the ecological exposure monitoring,
3 we used WARP to identify the watersheds that were most
4 vulnerable for atrazine exposure, based on WARP
5 estimates. The dark-blue watersheds you see here were
6 the ones that were the most vulnerable based on WARP.

7 And then what we did was have a
8 spatially balanced random selection process to identify
9 candidate watersheds for monitoring. And the results
10 of that study and through some of the followup
11 monitoring that is going on now are helping us better
12 define those vulnerable areas and how to target and
13 pinpoint those areas.

14 For the community water systems, the
15 approach was a little bit different, in that the
16 community water systems were identified based on Safe
17 Drinking Water Act monitoring on a quarterly basis.
18 The interesting thing is that most of those community
19 water systems that were identified -- and they're shown
20 as dots on the, on the map -- happened to fall into
21 that most vulnerable tier of watersheds; so that's more
22 reinforcement in terms of identifying vulnerability
23 based on something like WARP. So it does show that
24 there's ways to target the monitoring and that would be
25 more efficient in the way that where we have to target.



1 Both the models also targeted in time
2 with more intensive monitoring during the time period
3 coinciding with when atrazine was likely to be applied,
4 in this case to corn or sorghum, and continuing mostly
5 through the summer months in that regard.

6 For the ecological exposure monitoring
7 study, a subset of those sites included auto-samplers
8 to complement the regular 4 days' grab samples that
9 were taken at those sites, and that subset of
10 monitoring sites -- and they're not shown on there, but
11 they spread from Ohio, Indiana, Illinois and Missouri -
12 - that subset of sites are one of the subsets that
13 we're looking at because it provides daily or near
14 daily monitoring during the actual atrazine use area.

15 And that leads us to the second point,
16 which is the need for a set of intensively sampled
17 datasets. And we agree with the SAP's recommendation
18 that this is important.

19 For community water systems, the most
20 intensively sampled monitoring data we can find is
21 basically the weekly samples that we see that Syngenta
22 has been doing for the last several years with
23 community water systems here, and then there are a few
24 other precursor programs that also sampled weekly
25 during that regard.



1 We do know of some monitoring data that
2 is sampled more intensively. Heidelberg College, which
3 is now Heidelberg University, has been doing intensive
4 sampling in several streams of various sizes in Ohio
5 for a number of years, and so that provides a wealth of
6 data over time in one location where at least during
7 the likely times, times you're likely to find atrazine,
8 you have daily or near daily monitoring.

9 As I mentioned, the atrazine ecological
10 exposure monitoring program also had its subset of
11 sites that included daily or near daily sampling,
12 ranging primarily from April through the end of August.
13 That was spread out more over from Ohio westward to
14 Missouri and I think actually into Nebraska as well.
15 So it covers a little broader cross-section of the
16 atrazine use area. Some of those will have from two to
17 five years of data in that regard.

18 We think these datasets are critical for
19 determining confidence bounds in monitoring estimates
20 that help us to evaluate less frequent monitoring, and
21 what we're proposing to do is to use those datasets to
22 simulate different sampling frequencies to evaluate
23 what kind of confidence bounds we get in that with the
24 idea of possibly saying if you have, depending on what
25 your duration of concern is, a sampling frequency of X



1 days or X weeks might have a safety factor involved
2 associated with that.

3 We also think those are important if
4 we're looking at ways of estimating exposure in between
5 monitoring data points, and so this is a way for us to
6 evaluate how well those work.

7 As I've been talking about, we mentioned the Heidelberg
8 monitoring data and the atrazine ecological exposure
9 monitoring. Those are monitoring data for streams and
10 rivers.

11 We don't really have the same type of
12 daily or near daily monitoring for reservoirs. We're
13 looking at a couple of approaches: one, the streams and
14 rivers may use as a surrogate. We'd expect them to be
15 able a little more flashy in nature than what you'd see
16 in reservoirs.

17 The other is to use a model, pesticide
18 root zone model exposure analysis modeling system,
19 which is what we use to estimate our drinking water
20 exposures for reservoirs. It gives us daily
21 concentrations over typically 30 years of weather data.
22 So that's something we are considering as an
23 alternative for the reservoirs.

24 One issue that was raised at the last
25 SAP is whether drinking water treatment smooths out



1 those atrazine peaks so that treated water would be
2 less variable than the source water. What we know
3 about atrazine is that your conventional drinking water
4 treatment, which would be a process of sedimentation,
5 flocculation and chlorination, does not remove atrazine
6 from the water.

7 In general, you need an activated
8 charcoal treatment to remove atrazine from the water.
9 You can have, and activated charcoal can be used to
10 remove things like odor, it can remove things like
11 other organics other than atrazine. So the
12 effectiveness depends on how much you need and whether
13 you're targeting atrazine or something else.

14 What we did is we went back and looked
15 at 44 of the community water systems that had detects
16 of total chlorotriazines of 15 ug/L, and there's
17 nothing magical about that other than we wanted to
18 have a cutoff of looking at the more vulnerable systems
19 based on higher exposures, and that just seemed to be a
20 cutoff that worked given the time we had. So don't put
21 too much weight in that actual number; it was just to
22 help us get a manageable set of community water system
23 data.

24 We compared the paired source and
25 treated water samples for that, and what we found is



1 that for a third of those community water systems,
2 there was no difference in concentrations between the
3 source water and the treated water. For roughly half
4 of the systems, we saw some reduction in total
5 chlorotriazines as it went from source to treated
6 water; but it wasn't a complete removal. And roughly
7 about a sixth of the sites did we see complete removal
8 of the triazines as a result of treatment.

9 This plot here is an illustration of one
10 of the sites where the total chlorotriazines were
11 similar in both the source water, which you see in
12 blue, the blue and blue dots, and the treated water,
13 which is the magenta dots. So the bottom line, as you
14 see, it very much follows the same pattern.

15 The bottom line is that if we focus on
16 source water, it emphasizes, first of all, the
17 importance of protecting source water. Secondly, it
18 removes another potential source of variability that
19 you would have to account for whenever you're doing the
20 analysis.

21 But thirdly, it also reflects the type
22 of community water systems we see right here. So we
23 believe it's reasonably protective without being an
24 overkill. In those systems where the treatment does
25 knock out atrazine altogether, those can be addressed



1 separately in the risk assessment.

2 For terms of looking at variability,
3 though, this gives us a chance to use some ambient
4 water data and provide what we think is a reasonable
5 assessment of the type of variability you might see.

6 In the background document, we propose
7 assessing the uncertainty in the sampling frequency by
8 matching the weekly community water systems with the
9 more intensively sampled monitoring datasets.

10 And I want to try to explain what we
11 mean, because this is a comment we've wrestled with and
12 we still are asking ourselves: how well is this going
13 to work? But the idea is that for the community water
14 systems you have what we describe as a chemograph
15 shape, which looks at the number, the duration, the
16 spacing, the magnitude of your peaks or spikes that
17 occur during the monitoring season.

18 And the question we have is: can we
19 provide some general characterization of chemograph
20 shape or some classifications of chemograph shape where
21 we might be able to match a community water system with
22 weekly samples to one of the more intensively sampled
23 datasets.

24 And the idea is that if we can more
25 closely match these monitoring datasets based on



1 chemograph shapes, it may give us a bit more confidence
2 in analyzing the uncertainty bounds in that.

3 I do want to caveat this. We can start
4 with an intensively sampled dataset where you've got
5 daily or near daily samples, and we can create a
6 smoother chemograph based on, for instance, weekly
7 sampling. But you can't necessarily start with weekly
8 sampling and build in your daily peaks in between.

9 What we can do is that we can use that
10 intensively sampled dataset to provide some confidence
11 bounds of good exposure estimates we might see in
12 between.

13 So when we're talking about that, that's
14 where our thinking is. It is not to take a 7-day
15 sample and create this out of air but to provide some
16 confidence bounds in what we may have missed with the
17 sampling frequency, in this case the weekly sampling.

18 So we've done some preliminary analysis
19 on the intensively sampled Heidelberg and ecological
20 exposure monitoring datasets. We provided that
21 analysis in Appendix D2. I just want to touch on a few
22 things. I just point out what we did in this, we were
23 focused on that April to August time frame when we have
24 the most intensive sampling going on, and just for a
25 preliminary analysis we sampled those chemographs at 7-



1 day fixed intervals.

2 So we had seven separate fixed-interval
3 samples on that. And that's just to give us a feel for
4 whether we can work with that. If we were to do
5 further analysis then what we would really need to do
6 to simulate the way Syngenta did the monitoring on this
7 is to do bootstrapping analysis within weekly sampling
8 intervals, so it could occur at any time within that
9 regard.

10 Then what we also did is we compared the
11 number of spikes, the maximum detections. We also
12 looked at maximum 4-day average and the number of days
13 when those 4-day averages exceeded 20 to 40 ug/L.
14 These were numbers we just picked to work with.

15 These are not, once we determine the
16 magnitude and duration of concern, that's what we'll
17 ultimately work with; but this was just to give us an
18 idea of how we might work with that.

19 The numbers exceeding that period - as
20 a matter of fact, let me just go to the next slide.

21 Our thinking here is, particularly if
22 you're looking at something we know is not that one
23 peak exposure where you so you may have one day that
24 triggers the effect but it may be the period has to go
25 long enough until you get to your, as Dr. Rodriguez



1 explained, in a pseudo-steady state, then you probably
2 need more than one day to do that. So that's why we
3 are looking at the days where you might be exceeding
4 your, your, the threshold value, whatever it turns to
5 be.

6 This is a sampling from one year from
7 the Maumee River, part of the Heidelberg monitoring.
8 It's a relatively simple chemograph as far as those go.
9 You've got one large short-duration peak that's pretty
10 much driving your exposure, and you have a few smaller
11 peaks.

12 Just to get you oriented, the blue line
13 you see here is the daily concentrations measured at
14 this site. The dashed lighter-blue line are your
15 rolling 4-day averages. The red arrows point to the
16 peaks or spikes that we've identified in that
17 monitoring dataset.

18 Now if we are to take sampling at weekly
19 sampling intervals -- and what you see here, the red
20 dots show the weekly sampling intervals for one of the
21 seven potential intervals. The red line you see there
22 is just to help to see the shape of the chemograph.
23 What you do see is you start to see a little bit of
24 data-smoothing going here; you see some of the smaller
25 peaks are cut off, some of the valleys in between those



1 peaks are cut off, you get some smoothing.

2 If the sampling is timed right, though,
3 and this timing happened to hit your peak exposure, you
4 still get a shape that is fairly reflective of the
5 actual chemograph shape; however, if you were to take
6 those samplings, start those sampling intervals a
7 couple days later, you're likely to miss this short-
8 duration peak altogether, and in this regard, this is
9 what's driving your exposure. So if we were looking at
10 a short duration of concern, this would be missed
11 altogether.

12 And so this is one of the questions we
13 were asking in terms of doing this analysis: Can we
14 provide some type of a confidence bound around the
15 exposure estimates you get from weekly sampling; or
16 another way is some estimate of what's the probability
17 of missing the peaks of a certain duration of certain
18 exposure concentration?

19 I'm going to move to a little bit more
20 complex chemograph. This happens to be when you've got
21 two fairly large very short-duration spikes and a
22 number of smaller short-duration spikes that hit in
23 between, do not, you know, for now these actual
24 concentrations measured here are higher than what we've
25 seen in any of the community water system monitoring.



1 So we're not really concerned at this point about the
2 magnitude of the exposures; what we are concerned about
3 is how well we capture the actual exposure involved in
4 that.

5 In this particular area, you start
6 seeing, the more short-duration spikes you get, you
7 start seeing, even when you start capturing some of
8 these, there is still a lot of really small spikes,
9 peaks and valleys that are missed. And if you time it
10 right, it is possible even with 7-day intervals, which
11 we tend to think is a very robust monitoring data for
12 most pesticide, even 7-day intervals you can miss every
13 one of them, every one of those spikes.

14 This is the reason why we want to look
15 at more intensive monitoring datasets to get a feel for
16 what confidence we might have in exposure estimates
17 from less frequent sampling.

18 And I also point out that this is a good
19 example of one of the reasons that I think the April
20 SAP recommended that when you start looking at exposure
21 estimation methods, you need to look at methods that
22 have the possibility of estimating exposures that are
23 greater than the maximum that you measure. And so
24 these are some of the things that are driving where
25 we're going now.



1 So if we take a look at preliminary
2 analysis just to kind of sum up that section, the
3 chemograph shape, and particularly the duration of
4 frequency of the peaks and how much of an overlap we
5 get between peaks, whether they're separate or closer
6 together, it's very critical to sampling analysis that
7 we do.

8 As we look at this even with the more,
9 with 7-day fixed intervals, you can start, you can see
10 the effect of the data-smoothing, which comes back to
11 reinforce what the April SAP said and expressed as a
12 concern.

13 All that said, we believe that with this
14 analysis supports more strongly than before the need
15 for using intensive monitoring with daily sampling so
16 that we can get the expected during that expected
17 exposure period; so it's a critical to evaluate less
18 frequent monitoring samples and strategies in that
19 regard.

20 I want to close with an update on
21 approaches we've been looking at for estimating
22 exposures between sampling points, because we still
23 have weekly sampling. We've got a lot of years of
24 monitoring with weekly sampling. And we may find that
25 that weekly sampling interval is adequate if we can



1 provide some means of estimating exposures in between,
2 how best to estimate the exposures in between that.

3 We have a lot of pesticide monitoring
4 data for other pesticides where the intervals are even
5 longer, and a lot of monitoring 2-week intervals are
6 pretty good. A lot of NACWA monitoring tends to be in
7 2-week and some of the times you do get weekly, but 2-
8 week is more common.

9 One of the things that we understand and
10 the comment made by the SAP is the common methods we
11 use for interpreting between sampling intervals, which
12 is a linear interpretation or a stairstep-type
13 approach. They're likely to underestimate the peaks,
14 especially for the short-duration exposures.

15 We presented some ideas on using
16 artificial neural networks as a way of estimating
17 exposures. We haven't given up on that. It's possible
18 that they may still be too complicated for easy use,
19 but it hasn't been something we've given up on. We've
20 looked at some of the other recommendations in that
21 time frame.

22 The April SAP suggested looking at
23 extreme value theory. From what we've read and looked
24 at, it works best where we have a lot of measurements
25 over long periods of time.



1 We did find a paper by Huang and
2 Batterman that used both deterministic and still-
3 casting modeling to generate 1,000 years of data, and
4 then provided somewhat characterizing potential
5 exposures based on that. That may have some
6 application to what we're doing. It may also be
7 complex, but we are taking a look at that.

8 As far as kriging methods, kriging is
9 generally used for geospatial assessments, although it
10 does lend itself to temporal assessments because you
11 still have a, you have a similar autocorrelation-type
12 approach. It assumes a stationary mean and variance
13 that's critical.

14 The SAP recommended that we might
15 estimate the correlation structures across the pooled
16 systems, and your other recommendation which we're
17 looking at in more detail because we think there is
18 some real promise there is to combine it with a
19 regression model such as WARP.

20 So we've been looking at that. And
21 we've been looking at some of the USGS modeling
22 efforts, and there's some promise there that we're
23 following up on.

24 We've done some exploratory kriging
25 analyses using some of the intensive monitoring dataset



1 since we put out the background paper. And by "we", I
2 mean primarily Dr. Jim Hetrick and EFED did some of
3 this analysis, so I want to give him credit for doing
4 this work. I get to just be the talking head in this
5 regard.

6 I'm not going to try through the next
7 slide or two document what we did, but I want to use
8 what we've done to illustrate where our thinking is in
9 terms of next steps.

10 So we did a variogram analysis on log
11 transform data, and we found that the Gaussian
12 spherical models provide the best description of the
13 semi-variance structure. This is an illustration of
14 one year, but we looked over multiple years.

15 For those of you who may not be familiar
16 with the variogram analysis, the range refers to the
17 temporal scale where you have an autocorrelation within
18 the concentrations. So once you get beyond the range,
19 then we don't see a temporal relationship; it's more of
20 a random process.

21 But we did see in all the years, we saw
22 a strong temporal autocorrelation; it ranged from 35 to
23 83 days. And once again, this is using more
24 intensively sampled data than I think Dr. Lee looked at
25 with the weekly sampling at the last SAP.



1 We then estimated a time series using
2 one-dimensional, ordinary-point kriging, and this is
3 what you see here.

4 I'm going to step on to the next one,
5 because we then used a Gaussian sequential simulation
6 to assess the uncertainty associated with the missing
7 data. And we're only showing you the 50th, the 75th
8 and the maximum in this particular slide, which is I
9 think the one graph that does show up in the handouts
10 in that regard. So some of the lower percentiles, you
11 don't see plotted on here.

12 The conditional simulations generally
13 trace the actual monitoring data, and we would like the
14 fact that they do provide us a means of estimating
15 confidence bounds of data.

16 One issue that's critical not just to
17 kriging but to other exposure estimation methods is how
18 much information you lose when you go from frequent to
19 less frequent monitoring data, and what I'm going to
20 show you is a series of kriging data that started with
21 roughly the 4-day sampling, roughly weekly sampling and
22 then biweekly sampling, and you can see that by the
23 time you get to biweekly, this exposure profile really
24 didn't look anything like this.

25 At some point, that information loss



1 impacts not only our capabilities of estimating short-
2 term exposures, but it also impacts how well we can
3 estimate long-term exposures as well. So that's one of
4 the concerns we have as we move forward.

5 So to kind of wrap up what we're looking
6 at in terms of exposure estimation options, one of the
7 things we've talked about is the kriging looked
8 interesting, but we may get more information if we were
9 to do some type of co-kriging your concentrations with
10 something like daily stream flow. That may be helpful
11 in that regard.

12 The conditional simulations that are
13 based on monitoring data structure, particularly in
14 percentiles or some temporal structure, are very
15 critical in terms of providing some type of confidence
16 bounds that we can use to assess the monitoring
17 frequency.

18 We're looking very closely not just at
19 some of the updates of the WARP model. At the 2009 SAP
20 on atrazine ecological exposure, the SAP recommended
21 that we explore developing a corn-belt version of the
22 WARP model that incorporates more of the data, the
23 information available on a much more detailed scale
24 than on the national scale model.

25 I know there's efforts in USGS now on



1 looking at that corn-belt version of WARP, and so
2 that's something we are keeping our eyes on and keeping
3 in touch on with USGS, because we believe it has
4 applications not just for the ecological exposure but
5 also for community water-system assessments.

6 Even now, the WARP provides percentile
7 estimations that can be used in combination with
8 conditional simulations and we think there is some
9 promise there. One thing that came out, I think we may
10 have referenced this in the April SAP but we've taken a
11 little bit more look at this and talked to the person
12 in USGS who developed the SEAWAVE model, which was a
13 way of combining WARP with or, they're looking at
14 combining WARP with this seasonal variability model.

15 They use this model to assess trends
16 in assay concentrations over years, taking into account
17 the seasonal variability you get in rainfall and
18 runoff. They are looking at the potential of combining
19 this with WARP to provide more detailed monitoring
20 estimates.

21 One thing I will point out is that is
22 probably a little longer-term effort than we may be
23 looking at for a 2011 turnaround, so part of what we've
24 got to consider as we go forward is what can we do in
25 the immediate future.



1 So I promise this is the last slide.

2 So for drinking water monitoring portion
3 in this SAP, our questions are focusing on these main
4 issues. We've proposed a general framework for
5 designing a monitoring study that could be used to
6 estimate drinking-water exposures for range of exposure
7 durations of concern.

8 We've also made a proposal of what we
9 would like to do in terms of using intensively sampled
10 monitoring datasets to evaluate both various sampling
11 frequency strategies as well as other exposure
12 estimation methods. And we've updated our
13 considerations in terms of methods for estimating
14 exposure from less frequently sampled monitoring data.

15 So at this point I'm going to open
16 things up for questions.

17 **DR. STEVEN HEERINGA:** Thank you very
18 much, Nelson.

19 Questions or clarification from the
20 Panel? And first, Dr. Lee.

21 **DR. HERBERT LEE:** It's Herbert Lee, I
22 got two sets of questions. The first set is about the
23 variogram estimation you put up. What was the raw data
24 used to estimate that variogram?

25 **MR. NELSON THURMAN:** I think that was



1 actually one of the ecological exposure monitoring
2 profile sites. So it was one that had the

3 **DR. HERBERT LEE:** It was daily data?

4 **MR. NELSON THURMAN:** Daily data.

5 **DR. HERBERT LEE:** Looking at things like
6 the Heidelberg datasets, those don't look like Gaussian
7 correlation functions to me from ones I've seen,
8 certainly not a stationary Gaussian correlation
9 function itself. They're a lot less smooth. So I'm
10 surprised to hear you say that Gaussian looks
11 appropriate.

12 **DR. NELSON THURMAN:** Okay, and let me
13 clarify that we only looked at a small group. In fact,
14 I'm pretty sure I only provided Jim with the ecological
15 exposure datasets.

16 **DR. HERBERT LEE:** Okay.

17 **MR. NELSON THURMAN:** So that may very
18 well change when you look at the Heidelberg.

19 **DR. HERBERT LEE:** My second question is,
20 what do you mean by chemograph matching?

21 **DR. NELSON THURMAN:** What I mean is --
22 let me see if I can go back to that. I mean, naively I
23 thought that we could just say number of peaks with the
24 peaks might be a way of doing this; but what you soon
25 learn is that, what I've learned by this exercise is



1 when you start taking a look at weekly sampling, you
2 cut out a lot of the smaller peaks.

3 So I'm looking at more of a generalized
4 shape-type matching now rather than and probably more
5 generalized shape in terms of what is the duration of
6 your high exposure and whether there, how much overlap
7 do you see in that.

8 **DR. HERBERT LEE:** It seems like an
9 important thing to take into account there is the fact
10 that you may be missing peaks altogether when you're
11 matching those. But it's something that can be done.

12 **DR. NELSON THURMAN:** We learned that
13 very quickly, and if you have any suggestions on how we
14 might do this better, we're open to that, because the
15 more we looked at that, the more we saw holes in that
16 approach.

17 **DR. STEVEN HEERINGA:** Dr. Bailar.

18 **DR. JOHN BAILAR:** You're proposing to
19 collect some very extensive data, which will be
20 subjected to a quite sophisticated analysis. I'm
21 interested in the use of the output of that.

22 I see two broad categories of possible
23 use: one is what you could call scientific, trying to
24 understand the relationship between exposures and
25 health outcomes.



1 The second has to do more with
2 monitoring and surveillance over the very long run, and
3 I can see a use here of these data in deciding what
4 kind of monitoring and surveillance will be needed
5 during a long period of what might be regulation. Do
6 you see further uses of these data in the first of
7 those, the scientific category?

8 **DR. NELSON THURMAN:** Yes, I do see, and
9 I do want to clarify. We're proposing using extensive
10 data that has already been collected so we're

11 **DR. JOHN BAILAR:** Yes.

12 **DR. NELSON THURMAN:** In that regard, but
13 yes. And what we're proposing to do is take what can
14 we learn from that data. Our focus more is on what you
15 talk about the second part: how much monitoring, how
16 frequently do you have to monitor to do that; but at
17 the same time, there are scientific lessons that we're
18 going to learn from this that have a broader
19 application.

20 And the other thing I want to point out
21 is that we're actually requiring the registrant to
22 collect the data, so it's not EPA out there.

23 **DR. JOHN BAILAR:** Right, I understand
24 that and appreciate it; but I think this document might
25 be improved by having some further explanation of the



1 intended uses of these data and how you expect these
2 uses to play out over the years to come.

3 I have a second question that has to do
4 with sampling strategy. I understand how less frequent
5 sampling may miss the peaks; but still, if you have a
6 lot of samples, the peaks should be represented with
7 their frequency in the general population of possible
8 samples. So it's not clear to me why over a large
9 dataset you would miss the 1% kind of peak; it ought to
10 show up in 1% of your samples. Am I being clear?

11 **DR. NELSON THURMAN:** Yes, you are, and
12 one thing I want to say at this point, what we're
13 focusing on at this point, we're looking at individual
14 community water systems. So the concern is: is there
15 exposure on those community water systems that may be
16 exceeding what we, what would be determined to be a
17 level of concern in a year-by-year basis.

18 For the 90-day exposure period for those
19 sites we haven't had an exceedance in any of these
20 community water systems, but we've been looking closely
21 at that. If you look at this regard, our focus has
22 been on and once again, this is a condition of the re-
23 registration, because our assessment in general is, and
24 what you've explained, we have not been seeing
25 concentrations in general that have exceeded what we're



1 seeing at our existing level of concern; but at the
2 same time, we haven't seen some of the monitoring data
3 that is sampled more intensively.

4 So what we wanted to do as a condition
5 is have Syngenta go to those community water systems
6 that had higher estimate exposures from quarterly
7 samples, three of which are not likely to be in the
8 atrazine use period, and do more intensive sampling to
9 see whether that, those exposures are higher and how
10 much higher they are.

11 So that's where we have been going with
12 that. But our focus has been on the individual
13 community water system method.

14 **DR. JOHN BAILAR:** I think this aspect of
15 the sampling could also use some further explanation.
16 I'm not objecting to it.

17 **DR. STEVEN HEERINGA:** Other questions
18 and clarifications?

19 Dr. Lee, did you get all of your
20 questions in?

21 Yes, Dr. Krishnan.

22 **DR. KANNAN KRISHNAN:** In some of the
23 slides like 83 and other places, when you refer to TCT,
24 yes, it's atrazine as well as some of its
25 transformation products; and what other triazines are



1 also included and what's the approximate percentage?
2 Is there some idea of the range that you can give or
3 infer from historical data?

4 **DR. NELSON THURMAN:** All right. First
5 of all, it includes atrazine, simazine and the chloro-
6 degradates of --

7 **DR. KANNAN KRISHNAN:** DIA, DEA and

8 **DR. NELSON THURMAN:** Yes. So it
9 includes the chloro-degradates as well. I've been
10 working with basically the total TCT. The monitoring
11 data particularly in the last few years has not
12 analyzed for the individual components as well as the
13 total chlorotriazines, so we could go back and make
14 that estimate. One of the things we find is that it
15 tends to vary, depending on the timing and such and how
16 much degradation has occurred in there.

17 So it's not an easy straightforward,
18 "Here's what the percentage is". It's more of a range
19 over time. But we have not done that, but we have a
20 capability of doing that.

21 **DR. KANNAN KRISHNAN:** Also what I am
22 trying to understand is the atrazine assessment if it
23 is based on atrazine numbers at the end of the day,
24 would that be compared with the TCT monitoring data or
25 one liter atrazine, or would you add atrazine plus its



1 metabolites, if you can clarify that?

2 **DR. NELSON THURMAN:** We're focusing on
3 the TCT.

4 **DR. STEVEN HEERINGA:** Dr. Portier.

5 **DR. KENNETH PORTIER:** Maybe this thought
6 is not fully formed, but I'll ask it anyway. You
7 mentioned that in moving forward in designing a
8 monitoring plan, we needed to know about the dose and
9 duration, right, the area under the curve and how long.
10 It strikes me there's another aspect of sampling that
11 you haven't talked about, and that's the tolerance for
12 uncertainty in a decision.

13 You know, we use the phrase
14 "monitoring", and monitoring usually means at some
15 point I want to be able to answer the question kind of
16 with certainty that we have exceeded a certain level.
17 So we monitor to see when we exceed, right, and then
18 you can implement some kind of intervention.

19 An alternative is to measure and then be
20 able to come up with a probabilistic statement that
21 says, "Given what I've seen in these monthly
22 measurements, my chances of having exceeded this
23 criteria is such-and-such", right?

24 Now you haven't monitored, you haven't
25 measured that exceedance; you've measured something,



1 and through some kind of modeling or estimation
2 procedure you were able to make a probabilistic
3 statement.

4 Within the EPA scheme of things, is that
5 kind of second statement about a probabilistic chance
6 of exceeding, does that fit into the regulatory scheme?
7 Is that something that's thought about when you're kind
8 of designing the sampling scheme?

9 And the reason I'm talking about it is
10 because I think this is a key example of where you may
11 never be able to monitor enough, measure enough, to be
12 able to say with certainty that you've exceeded.

13 But you may be able to answer a
14 probabilistic statement with enough sampling to be able
15 to be confident that you exceeded a certain likelihood
16 of the event happening. I hope I'm clear enough.

17 **DR. NELSON THURMAN:** Yeah, and actually
18 we've talked about that in terms of that as an
19 approach. We didn't flesh it out much in the
20 background document and obviously didn't talk about it
21 too much other than, you know, one of the things I made
22 very brief mention and probably a lot briefer than it
23 should be in terms of our focus has been on: can we
24 try to find confidence bounds or some type of safety-
25 factor approach which plays in easier to what we've



1 been doing at FQPA.

2 But the other option is what's the
3 likelihood that we actually missed something of this
4 magnitude and this duration.

5 So it's something we've talked about in
6 some of the approaches, and I think extreme value is an
7 example of one where it may be easier to use it that
8 way.

9 So we have thought about that; we just
10 didn't flesh it out too much in that.

11 **DR. STEVEN HEERINGA:** Yes, Dr. Coupe.

12 **DR. RICHARD COUPE:** I'm Richard Coupe.

13 I just wanted to follow up a little bit on the
14 discussion we had the question before when you were
15 talking about mixtures of total chlorotriazines, and
16 this kind of brings up a little something I was going
17 to talk about later is that you'd have trouble going
18 back I think and looking at the total chlorotriazine
19 totals in historical data, because simazine was such a
20 big factor in days gone by and we no longer use
21 simazine. And so you wouldn't be able to do the ratios
22 very well.

23 The point that I wanted to bring up is
24 though, is that sometimes we seem to think that this is
25 all -- no offense to statisticians and whatnot -- but



1 it's not the same dataset every year. Things change
2 through time with market forces, and pesticides come
3 in, come out.

4 Sometimes it's not really easy to use
5 historical data. It's what you have right now which
6 you need to start with, but you need to always keep in
7 mind that these things are changing and the use
8 patterns and how you do it, adjuvants change; a lot of
9 things change that could mean every year you have a
10 different set of conditions out there that lead to an
11 exposure problem.

12 So you need to sample every minute of
13 every day.

14 **DR. STEVEN HEERINGA:** Any comments or
15 questions at this point?

16 I think if they come up, we'll have the
17 opportunity, of course, to address them again. Thank
18 you, Nelson and Mary, for this.

19 At this point, I think we're really
20 right on schedule with the program, which as I said is
21 an easy thing to do today; it'll be more difficult in
22 days to come. Forewarned is forearmed, I guess.

23 At this point in time, I think we return
24 back to Dr. Lowit for a presentation on Scientific
25 Considerations and Potential Sensitivity of Infants &



1 Children and Implications of the Mode of Action on
2 Water Monitoring Strategy.

3 **DR. ANNA LOWIT:** Well, if you'll give us
4 a minute, we're going to do some Musical Chairs.

5 **DR. STEVEN HEERINGA:** You can certainly
6 take your time.

7 **DR. ANNA LOWIT:** Ralph? I think it's
8 settled. I have a question for Dr. Heeringa. My
9 slides are, I have basically two short presentations,
10 about 10 or 12 slides. There's a natural stop in the
11 middle. I can either just do them all, or I can stop
12 in the center; either one.

13 **DR. STEVEN HEERINGA:** Why don't we stop
14 in the center and take a short break? No matter what
15 you do, we're going to be out of here early today, and
16 I don't want to drag this on unnecessarily today; but
17 why don't we go ahead and take a break in the middle
18 just for questions on it?

19 **DR. ANNA LOWIT:** Okay. Well, it's not
20 that many; it probably won't take that long.

21 So I did ask some members of the team to
22 come back up, because neither of these presentations
23 are heavy in data; they're more conceptual
24 intentionally. And so the people who know the answers
25 to the detail questions can be close at hand when those



1 come up.

2 Joe? Joe? Can you help me with working
3 the slides? It's like 20 of them or something.

4 So there are two presentations, and
5 they're coming up and we'll stop in between; but
6 they're both integrated, which is where we thought we
7 could sort of put them together.

8 **DR. STEVEN HEERINGA:** Go ahead and put
9 them together

10 **DR. ANNA LOWIT:** It doesn't matter.

11 **DR. STEVEN HEERINGA:** You're making a
12 convincing argument.

13 **DR. ANNA LOWIT:** Okay. Both topics have
14 both a hazard-assessment component and an exposures-
15 assessment component, and largely the issues as you
16 think about evaluating life stages and sensitivity are
17 not too far removed from how you think about the
18 critical duration. A lot of the same points come up,
19 particularly on the water. So it's moderately logical
20 to do this together.

21 So I'll start with the FQPA analysis.
22 FFDCA, as amended by the FQPA, or what should read the
23 Food Quality Protection Act, makes some unique
24 requirements of the Agency. And one of those is to pay
25 special attention to infants and children by thinking



1 explicitly about the availability of information on the
2 toxicology and the exposure of a particular pesticide.

3 And this relates to the FQPA safety
4 factor, the 10X factor. And for those of you who are
5 not familiar with our regulation it's a unique statute,
6 in that the Congress requires that we apply an extra
7 factor and that that factor can be removed in the event
8 that you have sufficient information for toxicology and
9 exposure.

10 At the present time, we have not
11 proposed a new FQPA factor. We have not revised the
12 factor from the red. We are reserving that decision
13 pending things that are still ongoing.

14 The chapter in the paper, in the Issue
15 Paper, has a lot of detailed information about
16 experimental toxicology studies, a short summary of
17 epidemiology which you heard from Dr. Christensen this
18 morning and is really missing in the water section
19 largely because, as you have heard from Nelson and
20 Mary, a lot of that work is still ongoing and still
21 being worked out.

22 So what I'm going to do in just these
23 few slides is instead of digging into the details of
24 the data, to talk to you more about the way we'll think
25 about the FQPA analysis and the kinds of things that



1 we'll think about. And so the question we're asking
2 the Panel is more around the framework of thinking
3 about those things, are we on target with the right
4 things, are we missing some things, that sort of
5 information.

6 So with respect to hazards, I'm going to
7 separate this. The bulk of this is going to be the
8 hazard considerations, because we've just spent, you
9 know, a good 45 minutes talking about the water so that
10 we don't have to duplicate that. So we'll circle back
11 around to hazard.

12 With respect to the hazard
13 considerations, the important issue to consider is the
14 availability of data to assess critical life stages.
15 And as I'll talk about a little bit more in detail in a
16 couple of minutes, there are some key studies that are
17 still ongoing that are pending.

18 But at the end of the day, we're going
19 to consider everything that we have available to us:
20 we're going to think about Mode of Action; we're going
21 to look at the animal toxicology database, the human
22 relevance of that data; we're going to look at the
23 dose-response relationships; and we're going to think
24 about the epidemiology findings.

25 So as we consider all the information



1 with respect to the Mode of Action, as I very quickly
2 gleaned over this morning, the key events involving the
3 neuroendocrine Mode of Action for atrazine have been
4 well established.

5 In 2000, the SAP supported those. It
6 starts with the effect of the pulsatile release of
7 GnRH, leading to changes in LH attenuation and
8 ultimately in the rat to mammary tumors, but in the
9 human we think more about development and reproductive
10 outcomes.

11 As you heard from Dr. Christensen this
12 morning, there is epidemiology data that is relevant
13 for thinking about infants and children. And we think
14 that this information provides qualitative evaluation
15 of the human relevance of some of the animal findings.
16 I think in particular, as you heard Carol talk about,
17 they're small for gestational age because we certainly
18 see changes in pup weight in the animal toxicology
19 base.

20 The two Farr studies on the menstrual
21 cycle effects as it relates, I think it's easy to think
22 about changes in LH attenuation affecting menstrual
23 cycle and, maybe to a little bit lesser extent, the
24 semen.

25 On the animal data, we did a fairly



1 extensive evaluation about it in the Issue Paper, which
2 is really the beginning of what will become a very
3 extensive sensitivity analysis.

4 We have right now a number of studies on
5 specific life stages: those from gestational exposure,
6 lactational, early postnatal and peripubertal. And
7 there are also two very recent high-quality tissue
8 dosimetry studies in fetuses and lactating pups, and
9 both of those studies actually come from EPA labs. One
10 of them is out of the Stoker lab.

11 The second one is a brand-new study,
12 which is a collaborative effort between Tammy Stoker of
13 NHEERL and one of the OPP analytical labs, so I think
14 that's a case where you collaborate across the Agency
15 to get very high-quality data.

16 We are putting a lot of focus on LH
17 attenuation as you've heard today, because it is well
18 documented with respect to dose and across lots of
19 different time courses from one day all the way out to
20 many months of exposure and, as Dr. Rodriguez
21 discussed, both the plasma concentrations and the LH
22 data we have. And you can correlate those very highly.

23 The LH attenuation is the most sensitive
24 endpoint of the database. No other high-quality study
25 provides endpoints lower than those from LH



1 attenuation, and that includes outcome data related to
2 delayed puberty onsets among other things, in addition
3 to the more standard guideline kind of studies we see
4 on systemic toxicity, such as dogs and rats and
5 everything else.

6 There is strong biological plausibility
7 with respect to LH attenuation, which makes it a good
8 endpoint for thinking about assessing human risk.

9 Okay. But one of the points of why we
10 are reserving the decision or a proposal around the
11 FQPA factor is there are three experimental toxicology
12 studies that are still ongoing -- and I mean ongoing,
13 still in the lab, animals still being exposed.

14 Two of these are at the ORD lab, the
15 first two of the bullets on the slide. The first one
16 is looking at hormonal changes and outcomes from
17 gestational exposure, and this will provide a nice
18 dataset. Right now there isn't a strong dataset
19 looking at hormonal exposure from gestation.

20 The ORD labs are also looking at
21 behavioral changes in male rats from gestational
22 exposure. The SAP report from 2000 on the key events,
23 as that Panel thought about the human relevance for
24 developmental and repro outcomes, there's a statement
25 in that report that neurobehavioral findings turn out



1 to be a sensitive endpoint. So ORD is looking at that
2 to see if that turns out to be true.

3 And then the third bullet is a study
4 being conducted by Syngenta, which I expect that or I
5 assume they'll talk about tomorrow, although I don't
6 know. But they're looking at the latent effects in
7 adults from both gestational/lactational exposure, and
8 that study is actually a direct result of some
9 uncertainty the Agency had identified in 2003.

10 And the statement is actually in the
11 Charge Question that one of the in the previous risk
12 assessment the Agency had identified multi-life
13 exposure studies as an area of uncertainty.

14 As I talked about a minute ago we have
15 gestational exposure, lactational, peripubertal, a very
16 isolated, but none that cover multiple life stages.
17 And as you think about people who don't move or a farm
18 family, let's say, that lives in Iowa and does that for
19 many years, that would be a multi-life stage exposure.

20 So the study that Syngenta's conducting
21 is, I believe, intended to fill that need of multi-life
22 stage. I expect them to talk about it tomorrow, so I'm
23 not going to spend a lot of time on it. We just
24 thought we'd let you know sort of how we saw the
25 status. It's a very complicated study. It has



1 multiple cohorts and multiple subsets. They're also
2 looking at recovery, which is very nice.

3 As of right now, as of July the 15th,
4 excuse me, two of the subsets have been submitted,
5 what's called Cohort I, Subset A, and Cohort II, Subset
6 D, which is essentially the gestational through
7 lactation and a postnatal through necropsy. So a great
8 deal of that study is still ongoing. I believe we'll
9 probably hear more about it tomorrow.

10 We are reserving our larger view of that
11 study, simply because so much of it is not in; but we
12 have made one observation so far that in the animals in
13 those two subsets that we've seen that there's a lack
14 of effect on LH.

15 The dose is less than 50 mg/kg, and as
16 you saw from Dr. Chester Rodriguez's presentation this
17 morning, that's actually a relatively unusual finding,
18 because even some of the other Syngenta data show
19 effects on LH at doses much lower than 50.

20 So that would be the hazard, the things
21 we'll think about for hazard: Mode of Action, dose-
22 response, epidemiology, human relevance. The other
23 part of the FQPA analysis is, it would be the drinking
24 water exposure.

25 And as you heard Nelson and Mary's



1 presentation, there's quite a bit of work to do in this
2 area. Part of it is because they're waiting for the
3 tox team to tell them what the duration is, and part of
4 it is it's just a very difficult issue that we're
5 working through.

6 But we are asking Questions 4.1 to 4.3,
7 and the answers to those will help us think about the
8 FQPA analysis.

9 So in the coming months, the Agency is
10 going to work, we're going to work towards completing
11 the scientific analysis for the FQPA factor. And what
12 we'd like from you in Question 5 is to think about
13 those factors I just talked about: the Mode of Action,
14 dose-response, human relevance, the findings and the
15 epidemiology, along with the thinking that will be the
16 responses to Questions 4.1 to 4.3: are we missing some
17 factors; does that seem like the right set of things to
18 think about; that sort of stuff.

19 Okay, so that's the FQPA issues. So if
20 we move on to thinking about putting it all together in
21 the water monitoring strategy, if we take a step back
22 and go back to the beginning.

23 The current drinking water program,
24 monitoring program that Syngenta conducts as a
25 requirement of registration that the Agency requires,



1 right now they're doing weekly monitoring during the
2 application and roughly the growing season, which is
3 roughly the spring to the summer, and biweekly for the
4 rest of the year.

5 In the last risk assessment, the Agency
6 conducted 90-day rolling averages of monitoring data,
7 and those averages were derived from interpolating
8 between the weekly monitoring points.

9 And I think the issue of interpolating
10 has been addressed in other comments; I'm just trying
11 to make sure everyone is on the same page of what was
12 done in the last assessment. So these 90-day rolling
13 averages were then compared against a level of concern
14 derived from the 6-month Morseth LH data.

15 So the question is: in this matching of
16 the 90-day rolling average to 6-month Morseth study,
17 given the current knowledge of atrazine, particularly
18 its temporality of the toxicology, should the critical
19 duration of exposure be revised and, if so, how?
20 That's the essence of this question.

21 So if we take another step back, it's
22 important to just say explicitly that the atrazine
23 database is lacking in human-specific information that
24 we can use to quantitatively extrapolate between rats
25 and humans.



1 Because of that, because of the lack of
2 real chemical-specific quantitative information, what
3 we have to do is to infer generic knowledge across
4 multiple disciplines. And so that's what we have done
5 and what we are asking for feedback on, because I
6 expect and I hope that there are more things that we
7 haven't considered, and that is what we ask from you.

8 So what we've done is we've looked at a
9 couple of different things. We're looking at the
10 empirical effects from animal studies and also
11 toxicodynamic and toxicokinetic information.

12 So if you go back to the toxicology
13 dataset for atrazine, there are a number of endpoints.
14 Delayed puberty onset is one of the major ones
15 throughout the developmental and reproductive dataset.
16 And in the rat, those studies are 4 days or longer; but
17 in humans, as we know, puberty occurs over a long
18 period of time.

19 So linking the 4-day exposure in the rat
20 from the LH study to the puberty in humans that lasts a
21 long period of time, there's a little bit of a mismatch
22 there.

23 As it relates to prostatitis, another
24 one of the endpoints measured in the atrazine database,
25 in the rat, exposure to the dam, when the dam was



1 exposed to atrazine there's an inhibition of prolactin,
2 transmission in the milk.

3 And it is this milk exposure to the pup
4 that affects the development of the TIDA neurons in the
5 offspring. And it is those TIDA neurons that in turn
6 cause the effect of the prostatitis in the male pups,
7 but it is derived from exposure to the dam.

8 In humans, prolactin plays a role in
9 development and maintenance of the prostate; but the
10 critical periods of development and the hormonal
11 involvement is far less known, particularly the
12 temporality of that.

13 Okay. So as we think about LH
14 attenuation, as the Cooper data have shown that we saw
15 from Dr. Rodriguez earlier, a single day of dosing is
16 not sufficient at low doses; at extreme high doses, you
17 may see some attenuation but not too much.

18 And to reach its maximal effect, we see
19 that at or around pseudo-steady state, which we believe
20 at the lower doses occurs around 4 days in the rat, and
21 that there is a very nice matching of this LH
22 attenuation beginning at 4 days to the pseudo-steady
23 state tissue levels also after 4 days. But the
24 question here is matching, matching this 4 days of
25 exposure from the LH in the pseudo-steady state in the



1 rat to the humans.

2 Pharmacokinetically, we much prefer to
3 use a PBPK model, as was alluded to earlier. McMullin,
4 there is a McMullin model out that we have reviewed
5 that we find has some important shortcomings. It does
6 not do a very good job of capturing the rapid kinetics
7 of atrazine and under-predicts the plasma
8 concentrations of the chlorotriazine metabolites.

9 Dr. Rodriquez did do a series of
10 calculations looking at and taking the elimination-rate
11 values from the Thede study and doing some allometric
12 scaling to see if that can't help inform durations of
13 exposure that would be relevant to humans.

14 So I won't do his calculations justice,
15 because he did them much better justice this morning;
16 but in essence what he has done is taken the
17 elimination-rate constants from the lower dose groups,
18 which are pretty constant across the 1- to 10-mg group,
19 and performed allometric scaling for an average female
20 body weight of 60 kilograms.

21 And he also assumed that there would be
22 three to five half-lives required to get steady state.
23 And if you look at this, the last column in here, you
24 see that the values range from something in the order
25 from about two-and-a-half weeks to about a month, maybe



1 four or five weeks, which all, despite the
2 uncertainties in the calculations, are all shorter than
3 the 90-day rolling averages currently being used.

4 So we also asked ourselves:

5 What is known about the LH surge in
6 humans that might inform critical periods of duration?
7 Dr. Mendez, who is not here now but was here this
8 morning, did some research into this area and found
9 that information from the pharmaceutical literature
10 might give us a qualitative handle on thinking about
11 windows of susceptibility in the human as it relates to
12 the menstrual cycle. I won't go into this in detail;
13 if someone wants to ask questions, they can ask Dr.
14 Cooper.

15 But our look at that literature is that
16 you can conceive from that IVF literature two different
17 periods of possible susceptibility. First would be the
18 follicular phase of the menstrual cycle, or in other
19 words approximately the first half of the female cycle,
20 or more specifically the second half of the late
21 follicular cycle, which would only last four or five
22 days.

23 It's very important as you think about
24 these IVF drugs and how they would relate the atrazine,
25 you have to be very careful not to put too much weight



1 on the absolute findings. IVF drugs are very potent.
2 They're given for very specific reasons. Most of them
3 are given by injection, they're not oral.

4 So there are some uncertainties around
5 making those comparisons. But we think qualitatively
6 they do suggest that the follicular phase, maybe even
7 the late follicular phase, is a potential window of
8 susceptibility.

9 So we have tried to think about this in
10 a multidisciplinary way, allometric scaling from the
11 pharmacokinetics; we've thought about the relevance of
12 the LH from rats to humans as it relates to the
13 menstrual cycle.

14 We've also thought about the
15 experimental toxicology data and the outcomes you see:
16 the delayed puberty, the prostatitis and how you would
17 relate those windows in the rat to the windows in the
18 human, and there really is no absolute finding. You do
19 see a range of possible values from that analysis of
20 just a few days, from four or five days up to something
21 in the order of for four or five weeks, maybe
22 approximately a month.

23 There are a couple of things you can
24 take from that. First, all of those are shorter than
25 the 90-day rolling average being used right now. There



1 may be other things we haven't thought of that are as
2 long as the 90-day rolling average. If there are, we
3 are looking for that feedback.

4 Another thing you can take from that is
5 that there is a lack of precision around the estimate,
6 and there is going to be a lack of precision in the
7 rat-to-human extrapolation. So what we'd like to do is
8 to have a multidisciplinary approach that thinks about
9 this from multiple points.

10 So as we think about answering Charge 6,
11 the Question No. 6, we'd like for you to comment on our
12 analysis -- I mean our preliminary conclusions -- but
13 we are also hoping that you have some alternatives and
14 some additional things for us to think about.

15 I think that may be the last slide in
16 this set, but both of these areas that I went over just
17 now, the FQPA analysis for the life stage sensitivity
18 and also the critical duration of exposure, not only
19 are they important as we think about the water
20 monitoring; but as we think about the 2011 SAP, they
21 will be the most likely two major areas on the hazard-
22 assessment side that we address at the next meeting.

23 **DR. STEVEN HEERINGA:** Thank you, Dr.
24 Lowit.

25 At this point, members of the Panel, any



1 questions of clarification on the material?

2 Dr. Fenner-Crisp.

3 **DR. PENELOPE FENNER-CRISP:** Most of the
4 studies that are still ongoing both in the Agency and
5 outside are focusing on the non-adult life stages. In
6 order to make conclusions about whether or not the
7 younger life stages are more sensitive than the adult,
8 do you have enough adult data against it to compare?

9 **DR. ANNA LOWIT:** I believe so, yes.

10 **DR. PENELOPE FENNER-CRISP:** For all of
11 the endpoints of concern?

12 **DR. ANNA LOWIT:** Yeah, I think that, I
13 mean, atrazine has a very strong database from really
14 top to bottom. I think when you add these datasets in,
15 they provide a very solid package from which to make
16 those findings, yes.

17 **DR. PENELOPE FENNER-CRISP:** What's the
18 timeline for finishing up the undone studies? Are they
19 going to be available by the time, your target time for
20 completing your reassessment?

21 **DR. RALPH COOPER:** Actually, there's two
22 papers in draft form at the moment, one addressing the
23 female and one addressing the male, wherein the dams
24 were treated from gestation day 14 through 21, they
25 were allowed to give birth, and then we followed the



1 offspring out, looking at a number of different
2 measures from body weight, most of your male
3 reproductive parameters.

4 There was some behavioral observations
5 in there, and we've gone on to look at some of the
6 parameters in the female that we look at typically in
7 cyclicity in that.

8 That study was run in four blocks, so
9 some of those offspring are getting up there in age and
10 we're waiting for them -- as a matter of fact, the
11 controls are undergoing reproductive senescence at the
12 moment. So this was a gestational only exposure;
13 that's the one that EPA was responsible for, or ORD.

14 And my answer to your question now is
15 imminent.

16 **DR. PENELOPE FENNER-CRISP:** That's good
17 news.

18 **DR. RALPH COOPER:** I hope that these two
19 papers are going through internal clearance within the
20 next couple of weeks, if I'm not overestimating how
21 hard those people are working.

22 **DR. ANNA LOWIT:** You can ask Syngenta
23 the same question on their study tomorrow.

24 **DR. PENELOPE FENNER-CRISP:** I will.

25 And the other question I have is, are



1 you open to the possibility there may be more than one
2 critical duration of exposure to have to decide what
3 kind of monitoring strategy you may have?

4 **DR. ANNA LOWIT:** We're open to your
5 feedback.

6 **DR. PENELOPE FENNER-CRISP:** Or you
7 wouldn't answer this question back in April. Is this
8 BMR going to be applied to all risk assessments from
9 acute through chronic, unlike the current one which has
10 a different dataset driving the acute?

11 **DR. ANNA LOWIT:** Just make sure we have
12 the terms right. The BMR is the response, make sure we
13 have the acronyms right. The BMR is the Benchmark
14 Response, which is the magnitude of the value in the
15 benchmark dose. So I think --

16 **DR. PENELOPE FENNER-CRISP:** It
17 represents a particular dataset.

18 **DR. ANNA LOWIT:** Yeah, so the benchmark
19 dose estimates that are in Appendix C, I believe, focus
20 on LH. As you accurately have said, the last risk
21 assessment, there were different endpoints for
22 different durations of exposure.

23 I think, I believe that what Dr.
24 Rodriguez has very elegantly shown in his overlay of
25 the temporal, the plasma data and the LH data is that I



1 think we need to rethink the durations of the risk
2 assessment, because if steady state or pseudo-steady
3 state around plasma levels are driving what the
4 responses are, particularly around LH, I think we have
5 to take a step back and look at those standard
6 durations that we normally use and maybe do something
7 or focus as it relates to the atrazine Mode of Action
8 from the toxicology data.

9 **DR. STEVEN HEERINGA:** Yes, Dr. Meek.

10 **DR. BETTE MEEK:** This is a really simple
11 question. It's just you mentioned that you weren't
12 proposing any change in the FPQA factor -- FQPA, sorry
13 -- at this time; but it was applied in the previous
14 assessment, the tenfold factor was applied? I just
15 want to make it clear.

16 **DR. ANNA LOWIT:** In the previous
17 assessment, it's in the Charge Question if you look at
18 the very beginning of the Charge Question. The
19 previous assessment for those systems included in the
20 community water system, the 10X was reduced to 3X,
21 because the drinking water monitoring was sufficient to
22 evaluate the 90-day rolling average.

23 **DR. STEVEN HEERINGA:** Additional
24 questions at this point?

25 I have one while others are thinking;



1 it's for Nelson. The auto-samplers, they're
2 accumulating samplers; they're not specific aliquot-
3 type

4 **MR. NELSON THURMAN:** Yes, that's true.

5 **DR. STEVEN HEERINGA:** Yes, Dr. Schlenk.

6 **DR. DANIEL SCHLENK:** I just had a
7 question. Maybe I should have asked it during the epi
8 presentation, but there were I guess some birth defects
9 that were associated with some of the epi studies, and
10 in reading the background documents, I guess there
11 wasn't a Mode of Action association with that.

12 I'm curious with the gonadotropin-
13 releasing hormone antagonist, has there ever been any
14 association with any birth defects associated with that
15 just to see if there's a common Mode of Action through
16 that pathway, and if that has or has been evaluated,
17 just--

18 **DR. ANNA LOWIT:** Well, I can add I'll
19 add the first part, and Ralph can add the second part.

20 To my knowledge that with respect to the
21 experimental toxicology database, there is some
22 standard rat in vivo developmental studies, and none of
23 those abdominal-wall defects have been seen. And they
24 can be seen in the rat, and they weren't. And some of
25 those doses in those studies are very high. But I



1 think Ralph had something to add.

2 **DR. RALPH COOPER:** Well, I was just,
3 with the GnRH antagonist, you can get pregnant, if I
4 understood the question.

5 **DR. DANIEL SCHLENK:** No, I'm just saying
6 with those particular compounds; I'm just saying
7 experimentally if you use those in a lower dose
8 obviously, they're very, very potent -- but could you
9 potentially generate a system that would allow you to
10 look at that potential endpoint and whether or not
11 those gut-wall issues are related to LH reduction or
12 not, if anybody's ever done that.

13 **DR. STEVEN HEERINGA:** Yes, Dr. Horseman,
14 you look like you're --

15 **DR. NELSON HORSEMAN:** This might relate
16 to the previous question. As I understand, all these
17 toxicology studies in gestation have been done in late
18 gestation. Has there been work done earlier in
19 gestation to look at outcomes of the pups?

20 **DR. RALPH COOPER:** To my knowledge,
21 early gestation alone actually, for a completely
22 different reason there was a study where the animals
23 were exposed for a little bit of different time on the
24 atrazine and they looked at outcome, and it was body
25 weight and blood pressure and these kinds of things.



1 I don't believe that work has been
2 published yet. It was actually done by another group
3 in RTP. But the Syngenta study that Anna showed up
4 there would be one where you would expose throughout
5 gestation; they started on gestation day 0, right?

6 And then there's multi-gen studies where
7 they do if there is a multi-gen on this, and I don't
8 know, I don't believe there was any such signals in
9 that study about effects in the pups there of that
10 nature.

11 And then of course there is the rat
12 developmental study that's required wherein the animals
13 are dosed from gestation day 6 to 16 or 6 to 20 I
14 guess, depending on the study; but 6 to 16 probably
15 given the age of the study, and they, for
16 teratogenicity there.

17 **DR. STEVEN HEERINGA:** Okay. What I
18 would like to suggest, Dr. Lowit, is that we take a 15-
19 minute break, and I know you have one wrap-up
20 presentation.

21 But talking with Joe Bailey, I think one
22 thing that would be productive, given that we have the
23 time today, we can't move on, unfortunately. I think
24 it would be nice to cover this in a little bit of time
25 this afternoon.



1 But what we can do is I'd like to go
2 sort of systematically through the Charge Questions,
3 not to discuss them but just to make sure that we
4 understand exactly what you're asking. And so we might
5 just click them off and say clear enough and we'll move
6 on; but we'll do that afterwards, and that'll benefit
7 our discussants, too, to make sure that, again, we
8 don't want to get into a discussion where we might sort
9 of influence your thinking, because I think that but
10 just to make sure that we understand the question
11 correctly and what you may be driving at there.

12 So we'll do that after the break. Let's
13 plan to reconvene at five minutes after 3:00.

14 **(WHEREUPON, a recess was taken.)**

15 **DR. STEVEN HEERINGA:** Okay, welcome
16 back, everyone. We'll wrap up our first day of the
17 FIFRA SAP meeting.

18 At this point, I mean, I turn the floor
19 back to Anna Lowit for the last of her presentations;
20 but I also think she had one point she wanted to
21 address from a break conversation we just felt that
22 should be brought out in the public discussion here,
23 too.

24 **DR. ANNA LOWIT:** And Dr. Krishnan and I
25 had a conversation; he approached me at the break



1 asking for clarification around how the total
2 chlorotriazines, i.e., the TCTs, are handled in the
3 exposure assessment. I thought it made more sense for
4 Nelson to do that than it did for me.

5 **DR. STEVEN HEERINGA:** Dr. Cooper is not
6 here, so it's Nelson.

7 **MR. NELSON THURMAN:** Sure. The water
8 monitoring data measured atrazine, simazine and each of
9 the chloro metabolites. And for what we were providing
10 in terms of exposure estimates has been on the sum of
11 the total chlorotriazines.

12 So that's how it's measured. If we find
13 at some point one metabolite is more toxic than the
14 other, we can go back and break that out, if necessary.
15 At this point, it makes sense just to do exposure
16 estimates on total chlorotriazines. Does that answer
17 your question?

18 **DR. KANNAN KRISHNAN:** Yeah. Thanks.
19 Based on I think where we are headed, I think that was
20 a critical question. I wanted to be sure that I I
21 know I had heard you almost around 2:30, but so I
22 wanted be sure that I have correctly get that
23 classification sort of thing.

24 **DR. ANNA LOWIT:** So just so we close
25 that loop, there is an implicit assumption there that

1 the Chloro metabolites are equipotent to parent
2 atrazine, and in the absence of really robust data to
3 do something more quantitative, it seems like a fairly
4 reasonable thing, particularly what's little - we know
5 a little bit about DACT and equal molar potency seems a
6 pretty reasonable assumption.

7 **DR. STEVEN HEERINGA:** Yes, Dr. Horseman.

8 **DR. NELSON HORSEMAN:** One tiny little
9 question, because I think it will come up tomorrow.
10 Hydroxyatrazine, which is apparently a bacterial or
11 plant metabolite, is it in any of these TCT
12 measurements?

13 **MR. NELSON THURMAN:** I was going to look
14 for Mary Frankenberry, who's dealt in it. I don't
15 recall that it is.

16 **DR. KANNAN KRISHNAN:** In the list of
17 components of TCTs listed in the document, it wasn't
18 listed.

19 **DR. STEVEN HEERINGA:** That was Dr.
20 Krishnan.

21 I guess if we can confirm -- I mean, if
22 we get information to the contrary, we'll

23 **MR. NELSON THURMAN:** Okay, yeah. If
24 it's not a chlorotriazine, then it would not have been
25 included, so .



1 **DR. STEVEN HEERINGA:** Dr. Lowit, I think
2 if we could have your last presentation, and then I
3 would like to go through this step of just walking --

4 **DR. ANNA LOWIT:** Okay, it's just a
5 couple slides to pull it all back together; there are
6 just three or four slides.

7 Just to go back to the very beginning,
8 we've covered a lot of very diverse topics today and
9 we'll have one more in the morning before the public
10 comments with Dr. Suzanne Fenton. We heard a very
11 detailed presentation from Carol Christensen on non-
12 cancer epidemiology today, and we'll have a couple of
13 questions on that.

14 We are proposing to continue to
15 emphasize LH attenuation in any future risk assessment,
16 as we believe this is a biologically plausible key
17 event in the Mode of Action for atrazine. As we see
18 the database, it's the most sensitive endpoint and
19 appears relevant for reproductive and developmental
20 outcomes, which are throughout the database.

21 We have conducted a number of series of
22 calculations since the April meeting around internal
23 dosimetry and benchmark dose analysis that you heard
24 about from Dr. Rodriguez.

25 And then drinking water, we have updated



1 the approaches. We provided some examples that you
2 heard from Nelson quite a bit ago.

3 The last two-part presentation -- I
4 don't know why that text is red -- that I gave a little
5 bit ago integrating the exposure and the hazard,
6 thinking about life stage sensitivity and the critical
7 duration of exposure. And both of those are components
8 for which we're still working and we're looking for
9 your feedback on, and will be a large bit of the focus
10 in 2011.

11 So thinking about the Next Steps around
12 non-cancer, pending the outcome of this meeting, we
13 anticipate a number of things in the coming months. We
14 anticipate selecting one or more or a range for that
15 matter of critical durations of exposure. And so
16 pending SAP -- put that S up there before you ask me
17 about the multiple ones. So certainly, we're thinking
18 about that.

19 And we'll be further developing the
20 drinking water analysis as you heard from Nelson, and
21 we'll be completing the FQPA analysis. We do expect an
22 SAP on these issues, along with any new studies that
23 come out in the literature, including those that have
24 come out since July the 15th, and we'll talk about
25 those in 2011.



1 Also in 2011, we'll move back to cancer
2 and cancer epidemiology. We are expecting sometimes in
3 the coming months a new study from the Agricultural
4 Health Study on cancer, and that will be integrated
5 along with other cancer epidemiology studies in the
6 experimental toxicology database on cancer, and we'll
7 also cover that at the 2011 meeting.

8 And I think that's it, yep.

9 **DR. STEVEN HEERINGA:** Okay. Thank you
10 very much.

11 At this point, what I would appreciate
12 and I think it would be useful; we often do it
13 concurrently just but I think since we have a little
14 time, if we could bring up the Charge Questions and
15 just step through those.

16 I don't think we'll spend a lot of time.
17 But if you would, Dr. Lowit, just sort of try to
18 paraphrase essentially what in the intent of that
19 question is. Most cases it will be very obvious, but I
20 think there are some times where we've had situations
21 where what you intended and what our people read into
22 it were slightly different.

23 So if you could do that now, it
24 certainly will prepare us for tomorrow afternoon or
25 Thursday morning as we begin to address the Charge



1 Questions.

2 So, again, you can make this as short
3 and sweet as you'd like. If you think it's very clear
4 what you're asking for, just .

5 **DR. ANNA LOWIT:** Well, we always think
6 it's clear; but sometimes it turns out to not be that
7 way. So this is probably a very good idea. And I've
8 asked the major leads on each particular subsection to
9 come up; so if I misspeak on our question for that or
10 if there's anything to add, we'll do this as a team
11 effort.

12 The epidemiology, we have two sub-
13 questions. The first one is largely on our reviews and
14 that to give us feedback on whether or not our reviews,
15 particularly in the Appendix, do an adequate job of
16 identifying the major strengths and limitations of
17 those studies. So I think the source of that
18 information is predominantly in the Appendix.

19 **DR. STEVEN HEERINGA:** Dr. Gold and her
20 discussants are prepared to address that, I'm sure.

21 Sure, if you'd like to.

22 **DR. ELLEN GOLD:** So one thing we were
23 wondering is if you want comments on each specific
24 study or if you want more generic kind of comments
25 about strengths and limitations that might not have



1 been touched on.

2 **DR. ANNA LOWIT:** I think it depends; I
3 think that's largely up to you. We're not going to
4 tell you how to answer the question. There are
5 multiple ways to cut it.

6 **DR. STEVEN HEERINGA:** Right. I think we
7 have the detail and that will be in the written report,
8 and the question is whether we go individually through
9 the studies; but we can discuss that more, but I think
10 the intent of that question is quite clear.

11 **DR. ANNA LOWIT:** Go ahead.

12 **DR. STEVEN HEERINGA:** Dr. Christensen.

13 **DR. CAROL CHRISTENSEN:** Yeah, this is
14 Carol Christensen, so just very briefly. I guess
15 specifically with those five evaluations that I had
16 sort of characterized as being somewhat stronger across
17 the database; so comments individually on those studies
18 in particular would be helpful.

19 In my slide presentation and also within
20 the written evaluation, sort of identified those on
21 female/male reproductive health and small for
22 gestational age.

23 These are the ones that we are
24 characterizing as being relatively stronger across the
25 database. So it's the two Farr studies, the State of



1 Illinois and the Villanueva - I'm sorry, it's Ochoa-
2 Akuna. It's in my slide presentation.

3 **DR. STEVEN HEERINGA:** So from this
4 morning, there are five studies in particular that you
5 would appreciate individual comments, okay. I think
6 there are 14 other studies total that you considered?
7 Maybe Question

8 **DR. ANNA LOWIT:** Okay, Question 1.2 has
9 two subparts, and admittedly there is some overlap
10 between A and B. But they're intended to get at
11 specific sections in the Issue Paper. The latter part
12 of Section 3 describes the utility of the epidemiology
13 database as it relates to risk assessment, and that's
14 what's in Part A.

15 And then, Part B focuses primarily on
16 what's in Section 4 of the Issue Paper, which is
17 thinking about bringing the strengths or similarities -
18 - the strengths, the differences and the uncertainty in
19 both of the experimental toxicological and the
20 epidemiology databases together in one integrated
21 analysis.

22 So admittedly, there is some overlap
23 between A and B; but they are separate sections of the
24 Paper, so we had separate sub-questions.

25 **DR. STEVEN HEERINGA:** John, are you



1 fairly comfortable with Part 1.2?

2 Dr. Gold?

3 Okay, thanks. So, Question 2.1.

4 **DR. ANNA LOWIT:** Okay, the large
5 subheading of Question 2 relates to mammary gland
6 development, and there are also two parts here.

7 The first one relates primarily to the
8 two Rayner papers and the Coder paper, which is one of
9 the Syngenta-supported papers. The Rayner, the two
10 Rayner publications come out of the Fenton lab.

11 And we find as we look at those there
12 are some similarities; but there are also some
13 differences, and we are looking for some feedback on
14 what could lead to some of those, the differences in
15 those findings, and similarities for that matter.

16 **DR. STEVEN HEERINGA:** Dr. McManaman,
17 fairly comfortable with those questions as you
18 understand them?

19 **DR. JAMES McMANAMAN:** Yeah.

20 **DR. STEVEN HEERINGA:** Good, thank you.
21 Yeah, a confident response, that's good. I like that.

22 **DR. ANNA LOWIT:** Question 2.2 is
23 explicitly about the Enoch mixture paper. As I noted
24 very briefly in my introductory remarks, if you look at
25 our review in Appendix A, we have some concerns about



1 that study and are having some trouble interpreting
2 that study.

3 And so that's what Question 2.2 is
4 getting at: not only a review of the strengths and
5 limitations, but in your view how the study design
6 impacts the interpretation. So it's predominantly a
7 mixture question, but I think some of the mammary gland
8 development issues are also implicit in that.

9 **DR. STEVEN HEERINGA:** Dr. Mumtaz?

10 **DR. MOIZ MUMTAZ:** That should be good.
11 You want to focus only on the mammary glands, is that
12 right, Anna?

13 **DR. ANNA LOWIT:** Just the Enoch paper.

14 **DR. MOIZ MUMTAZ:** Yeah, right. And then
15 look at the experimental design. I'm comfortable with
16 that.

17 **DR. STEVEN HEERINGA:** Good, thank you,
18 sir.

19 Question 2.3.

20 **DR. ANNA LOWIT:** Yes, and then there is
21 one more as it relates to mammary gland development.
22 It is thinking about integrating the mammary gland
23 development papers into the weight of the evidence for
24 atrazine.

25 We are, as you heard earlier, choosing



1 to emphasize more of the LH attenuation and use the
2 mammary gland development more in hazard
3 characterization as opposed to hazard identification,
4 and we're looking for feedback on that proposal.

5 **DR. NELSON HORSEMAN:** If Jim and Moiz
6 make it easy, it will be easy.

7 **DR. STEVEN HEERINGA:** Okay, Dr.
8 Horseman.

9 Okay, Question 3.1.

10 **DR. ANNA LOWIT:** I keep forgetting to
11 advance the slides.

12 Okay. Then we have a series of smaller
13 questions intended to get at particular components of
14 the tissue dosimetry and the proposed updates to the
15 dose-response assessment. And we had hoped that we had
16 written them so that there was a logical order that one
17 would build on the other, but I'm sure there's a good
18 bit of overlap.

19 The first one has to do with simply the
20 non-compartmental analysis conducted by the Agency that
21 you heard from Dr. Rodriguez this morning to estimate
22 internal dose of atrazine and its metabolites.

23 **DR. STEVEN HEERINGA:** Dr. Greenwood?

24 **DR. RICHARD GREENWOOD:** No, I think
25 that's clear. Obviously, there will be some overlap



1 with other things; but I think that that's clear, thank
2 you.

3 **DR. ANNA LOWIT:** So I think that the
4 difference between A and B, A is more the actual
5 analysis and the mathematical procedure behind the
6 analysis, and Part B is a related question asking about
7 our interpretation of what is Figure 5.5 in the Issue
8 Paper which we saw a couple of times today, which is
9 the figure from the Thede paper of the tissue dosimetry
10 data of the ramping up, and the values stay fairly
11 constant until they stop dosing and they're eliminated
12 and our interpretation of what that figure shows.

13 **DR. STEVEN HEERINGA:** We're set there;
14 Dr. Krishnan indicates that we're all set on that one,
15 too, in terms of our understanding of what you're
16 after.

17 **DR. ANNA LOWIT:** Okay. And then we have
18 two sub-questions on the benchmark dose analysis. The
19 first one is akin to the first one of 3.1; it's more of
20 a technical review of the actual analysis, the things
21 contained in Section 5.3 in Appendix C.

22 And then the Part B of that one is more
23 of a conceptual subpart around establishing a benchmark
24 response as it relates to calculating benchmark doses.
25 So one is a technical mathematical question, and the



1 other one is mostly conceptual.

2 **DR. STEVEN HEERINGA:** Parts A and B, Dr.
3 Meek, are you, and then Dr. Roby?

4 Okay, great. Okay. I guess 4.1, Dr.
5 Lowit.

6 **DR. ANNA LOWIT:** Okay. Then we have the
7 next one in that wait a minute. Now, I'm confused.
8 The slides are like out of order or something.

9 **DR. STEVEN HEERINGA:** I think I jumped
10 you over.

11 **SPEAKER:** 3.2 is 2.

12 **DR. STEVEN HEERINGA:** Yeah, we did 3.1.A
13 and B, and I think we did not do we did C and then I
14 jumped ahead here. So, Dr. Akana on 3.1.C.

15 **DR. ANNA LOWIT:** So we, the Agency, we
16 need to fix these slides. C is missing from the slides.
17 Okay, so it's just out of order. Okay.

18 So this subpart, whichever number it is
19 I'm moving too fast to figure out, but this is a
20 subpart question. I think it's the one after Figure
21 5.5, but it doesn't matter I guess for right this
22 second.

23 We do have a sub-question around our
24 interpretation of what is Figure 5.5, which was
25 discussed at length this morning after Dr. Rodriguez's

1 presentation, and it is the overlay plot of the LH
2 attenuation data from I believe it's four studies --
3 the new Cooper data; the Morseth 6-month data; and a
4 couple of other studies -- and that the analysis that
5 went into that plot and our interpretation of it.

6 **DR. STEVEN HEERINGA:** Yeah, we have this
7 question as 3.1.C, and Dr. Akana is our lead
8 discussant.

9 **DR. ANNA LOWIT:** Okay, we'll have to fix
10 these tonight, the slide numbering.

11 So I believe that covers all the dose-
12 response, even though they're out of order. And I'll
13 let Nelson cover his.

14 **MR. NELSON THURMAN:** Okay, Question 4.1
15 is basically focusing on what we propose as the
16 framework for the monitoring study design; so more or
17 less wanting to get your feedback on strengths,
18 weaknesses, anything else you'd want to recommend on
19 that.

20 **DR. STEVEN HEERINGA:** So Wesley Stone on
21 Part A, are you okay with that, Wesley, and then on
22 Part B

23 **MR. NELSON THURMAN:** Okay, and Question
24 4.2 is

25 **DR. STEVEN HEERINGA:** Oh, Dr. Coupe on

1 4.1; yes, I'm sorry. 4.2, I'm sorry.

2 **MR. NELSON THURMAN:** Okay. 4.2 is
3 basically questions relating to our plan to use the
4 intensively sampled monitoring data.

5 And the question on chemograph shapes,
6 we already heard some question about what we're
7 intending, and I hope I clarified that a little bit.
8 But that is something the more we put together, the
9 more difficult the concept and application is. So
10 we're interested in your feedback on that.

11 And then the second's on the strengths
12 and weaknesses of the data that we propose using.

13 **DR. STEVEN HEERINGA:** I think Wes is
14 indicating he's good with Part A.

15 **DR. WESLEY STONE:** On Part B, can you
16 say that again in terms of what you're looking for?

17 **MR. NELSON THURMAN:** On Part B, we're
18 looking for the strengths and weaknesses of the
19 datasets themselves. The Heidelberg data, the
20 ecological exposure monitoring data. And then I
21 touched on it briefly, but the idea of using prism
22 exams for reservoirs, as opposed to the --

23 **DR. WESLEY BROWN:** Okay, so it's about
24 the data themselves, because it wasn't clear. It's
25 using them for something in particular or just using



1 them in general or--

2 **MR. NELSON THURMAN:** Well, using them
3 for evaluating the sampling frequency and the model
4 estimation.

5 **DR. STEVEN HEERINGA:** And there is a
6 Part 4.3, too.

7 **MR. NELSON THURMAN:** Yes, there is, and
8 4.3 is what we had recommend, their update on base
9 basically how we might estimate the exposure
10 estimation, what methods we'd use to estimate exposures
11 in between.

12 **DR. STEVEN HEERINGA:** Dr. Lee indicates
13 that he comprehends and we addressed that.

14 Question 5, then, I guess we go back.

15 **DR. ANNA LOWIT:** Questions 5 and 6 are a
16 little different than I think all the other questions;
17 they're more conceptual and a little bit more esoteric
18 than some of the other ones that are far more
19 technically oriented.

20 The first, Question 5 on the scientific
21 considerations for potential sensitivity, that was the
22 first half of my presentation this afternoon. And what
23 we're asking you to provide us feedback is on the sorts
24 of scientific factors we should think about as we move
25 forward with an updated FQPA 10X analysis, keeping in



1 mind that we're going to be that there's particular
2 focus under FQPA to infants and kids, and we'll be
3 thinking about things like that I had in my slide: the
4 drinking water, sufficiency of the drinking water data;
5 the Mode of Action; the epidemiology; the human
6 relevance; all the things that were in my slides and
7 that are in that chapter of the Issue Paper. So it's
8 predominantly a bigger-picture question around the
9 factors to think about.

10 **DR. STEVEN HEERINGA:** Carey, Jan, Bette,
11 Penny, are you okay with that in terms of the way it's
12 okay.

13 **DR. ANNA LOWIT:** And then Question 6 is
14 the one that's intended to bring everything together as
15 we think about the critical windows of exposure or the
16 duration of exposure for moving forward with a risk
17 assessment or as we think about the monitoring
18 frequency.

19 We've thought about it in a number of
20 ways I talked about earlier, and we're asking you to
21 not only comment on what's in our Paper that we've
22 already done and the sorts of things that we're
23 thinking about, but also to provide alternatives and
24 additional things to think about, because this will be
25 one of the areas that we put a good bit of emphasis on



1 in the coming months.

2 **DR. STEVEN HEERINGA:** Dr. Bucher,
3 associate discussants? Do you feel comfortable with
4 it?

5 Dr. Coupe?

6 Okay. I think it appears that we're all
7 set there. Anything from the Panel? I appreciate
8 taking the time to do that. I think that hopefully
9 will be helpful.

10 Okay, at this point in time, in the
11 Agenda we have completed the scientific presentations
12 from the EPA. We'll have an opportunity first thing
13 tomorrow morning to I think Dr. Lowit and the team, if
14 you have anything that occurs to you overnight you want
15 to present, you'll have an opportunity first thing.
16 But we'll also have a presentation tomorrow morning by
17 Suzanne Fenton of NIEHS.

18 And after that presentation and our
19 questions of clarification, we'll move to the period of
20 public comment. If there's anyone in the audience who
21 wishes to make a public comment, please see Joe Bailey,
22 the Designated Federal Official, to sign up for a time.

23 One other comment I guess, public
24 comment I think will take a substantial share certainly
25 of the late morning and afternoon, I believe. There



1 will be a number of presentations, and several of them
2 will be fairly lengthy and in-depth.

3 So we'll spend the time we need to focus
4 on that. But for public commenters, slides, make sure
5 that they are brought to Joe or to the SAP Staff to be
6 loaded up, hopefully before your presentations, or if
7 you have handout material see that they get to Joe also
8 so that he can arrange to have them copied and
9 distributed.

10 There is one handout that the Panel has
11 received. It's a preliminary view and statistical
12 analysis of data associated with Cooper, et al., study
13 by Dr. Silken and I think this may be relevant to some
14 of the public comment tomorrow; but just note that the
15 Panel has received it, and a copy of this will also go
16 into the Docket.

17 Okay, at this point, are there oh, Dr.
18 Lowit.

19 **DR. ANNA LOWIT:** Just one issue about
20 the first thing in the morning, we're still working to
21 get Dr. Fenton's slides. Our hope is that by 8:30, we
22 have 30 copies of them. They may appear while she's
23 talking if we don't get them in time, but we're doing
24 our best.

25 **DR. STEVEN HEERINGA:** That's fine; we



1 understand.

2 **DR. ANNA LOWIT:** She just came back from
3 Spain a couple of days ago, so

4 **DR. STEVEN HEERINGA:** I'll have to use
5 that one, just came back from Spain.

6 **SPEAKER:** For you it's Russia.

7 **DR. STEVEN HEERINGA:** Yeah, Russia.

8 Okay. And just a note from Joe Bailey, too, we will
9 start tomorrow morning at 8:30. Barring any other
10 questions from the Panel this afternoon again, you'll
11 have a chance tomorrow morning first thing, too, and
12 probably throughout the session tomorrow -- but I think
13 we'll bring the afternoon's proceedings to a close.

14 Panel members, if we could just meet
15 briefly in the breakout room just to discuss any sort
16 of small group sessions that you may want to plan in
17 preparation for addressing the Charge Questions,
18 probably later tomorrow afternoon or certainly first
19 thing Thursday morning.

20 So, if not, good afternoon, everybody,
21 and we'll see you 8:30 tomorrow morning.

22 (WHEREUPON, the MEETING recessed for the day at 3:32
23 p.m.)

24

25



CAPTION

The foregoing matter was taken on the date, and at the time and place set out on the Title page hereof.

It was requested that the matter be taken by the reporter and that the same be reduced to typewritten form.

Further, as relates to depositions, it was agreed by and between counsel and the parties that the reading and signing of the transcript, be and the same is hereby waived.



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2 COMMONWEALTH OF VIRGINIA

3 AT LARGE:

4 I do hereby certify that the witness in the foregoing
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7 first being duly sworn to testify the truth, the whole
8 truth, and nothing but the truth; and that the said
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12 transcript as taken, all to the best of my skill and
13 ability.

14 I further certify that the inspection, reading and
15 signing of said deposition were waived by counsel for
16 the respective parties and by the witness.

17 I certify that I am not a relative or employee of
18 either counsel, and that I am in no way interested
19 financially, directly or indirectly, in this action.

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22
23
24 MARK REIF, COURT REPORTER / NOTARY

25 SUBMITTED ON SEPTEMBER 14, 2010



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